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The Dynamics of Racial Intermixture—an Analysis Based on the American Negro

BENTLEY GLASS

The Baltimore Rh Typing Laboratory, and The Department of Biology, The Johns Hopkins University

and

C. C. LI

Graduate School of Public Health, University of Pittsburgh

INTRODUCTION

So far as we are aware, gene frequencies have not been used to study the *dynamics* of the process of "racial" or population intermixture in the human or any other species, although many studies have dealt with static and historical aspects of hybridization. The distinctive characteristic of the investigation of the dynamics of such a process is that it is concerned primarily with the *rate* of the process and the establishment of dynamic equilibria, rather than being concerned merely with past or present gene frequencies and amounts of intermixture. It is, of course, an understanding of the dynamics of the process that most fully illuminates its past and has greatest predictive value for the future. It will be of great help in investigating a variety of social and anthropological problems to know something about the rates of intermixture between populations and the positive or negative acceleration of those rates. It is our hope that in the present paper the authors have made a modest beginning in the application of such methods to human problems.

The necessary data consist of determinations of allele frequencies in the several populations involved, that is to say, in the base populations and the hybrid population formed by their intermixture. The simplest situation to analyze would obviously exist where only two base populations were intermixing, a situation such as occurs in North America, where the American Negro population has been formed largely by the intermixture of a pure Negro population and a European White population. In fact, the authors' interest in the problem stemmed originally from the observation of the enormous difference between the frequency of the blood type Rh_0 (cDe) reported to prevail in American Negroes, in contrast to the low frequency which is characteristic of European and North American White populations (see Table 1). How could so great a difference exist after generations of so much introgression

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of genes from the white into the Negro population as is commonly assumed to have occurred? The situation was somewhat clarified when data became available on the Rh_0 frequency in African Negro populations (Table 1). The American Negro population is now seen to be intermediate in frequency, and closer to the African Negro frequency than to that of the North American white population. A formula was suggested by Bernstein (1931) which might be applied to such differences in order to calculate the amount of racial intermixture which has occurred, and his method has since that time been applied in numerous instances (e.g., Boyd, 1939b; Wiener, 1943; Ottensooser, 1944;

TABLE 1. Rh_0 FREQUENCIES

AFRICAN NEGRO	N. AMERICAN NEGRO	N. AMERICAN WHITE	W. EUROPEAN WHITE
S. African Bantu[1]	N. Y. City[4]	N. Y. City[4]	English[8, 9]
769–64.07%	223–41.7 ± 3.3%	1000–2.6 ± .5%	1798–2.17%
			1038–2.31%
E. African[2]	N. Y. City[5]	N. Y. City[5]	French[10]
?–ca. 64.0%	135–45.9 ± 4.3%	335–2.69 ± .9%	1000–3.00%
Ewe—W. Africa[3]	Baltimore[6]	Brooklyn, N. Y.[7]	Dutch[11]
853–63.4%	907–43.8 ± 1.65%	7317–2.2%	995–1.47%
			Italian-Milan[12]
			357–2.24%
			Italian-Ferrara[12]
			406–1.5%

[1] Shapiro, 1951.
[2] Donegani, Ibrahim, Ikin and Mourant, 1950.
[3] Armattoe, 1950.
[4] Wiener, Belkin, and Sonn, 1944.
[5] Levine, 1945.
[6] This paper.
[7] Unger, Weinberg and Lefkon, 1946.
[8] Race, Mourant, Lawler, and Sanger, 1948.
[9] Murray, 1946.
[10] Bessis and Gorius, 1949.
[11] van Loghem, Bartels, and Hart, 1949.
[12] Morganti, 1948.

da Silva, 1948, 1949; Boyd, 1950a, 1950b; Laughlin, 1950). The formula may be expressed as follows:

$$\frac{q_x - Q}{q - Q} \times 100$$

where Q and q are the allele frequencies for a particular allele in the base populations, and q_x is that in the hybrid population. While such an expression is of value in comparing populations representing different admixtures of the same base populations, as Stevens has done (1952), it tells nothing of the dynamics of the process, since it assumes that the intermixture occurred all at once, that is, in a single generation; and thus it gives the accumulated amount of intermixture, regardless of the rate of gene flow between the populations. For example, applying it to the data on the Rh_0 frequencies, we learn that the amount of intermixture in the American Negro population is equivalent to 35.4

per cent of genes from the white population, if we take Wiener's value for the Rh_0 frequency in the American Negro, and 28.4, if we take Levine's figure. This, while interesting, tells us nothing about the dynamics of the process of intermixture.

THE ALLELE FREQUENCIES

Before describing the model from which the expression for the dynamics of the process is derived, it will be well to consider first the nature of the data required for its application to concrete situations. These data are the allele frequencies in the base and hybrid populations.

It is clear that the most reliable results will be obtained when the base populations differ most widely in the frequencies for a given allele. For this reason the determinations based on the R^0 frequencies ($Q - q = .60$) will be much more reliable than determinations based on the frequency of I^A ($Q - q = .095$) or I^B ($Q - q = .096$). For every determination of an allele frequency involves a sampling error related inversely to the square root of the size of the sample, and where the difference between Q and q is small, the sampling errors are relatively larger. For small differences of allele frequency between populations the standard error of the difference, unless based on enormous numbers of individuals, will approximately equal or exceed the difference itself in size. That is to say, the coefficient of reliability (t) will be very low.

These considerations emphasize the importance of having the determinations of allele frequencies based on adequate samples of the populations being studied. It is a commentary on the failure of geneticists and serologists to act on this understanding, that although the first samples of American Negro bloods were subtyped for Rh with three antisera in 1944, no further data have been reported since those of Wiener, Belkin, and Sonn (1944) and of Levine (1945). Yet these preliminary reports were obviously inadequate as samples of the American Negro population, first of all because of their small size and consequently large standard errors; and secondly, because both samples were taken from the New York City Negro population, which may differ considerably in its allele frequencies from the Negro population in other parts of the United States. In addition, a third possible source of error may be pointed out. Care must be taken to ensure that the individuals classified in any sample are truly a random sample of the population to be studied. In clinical work this is often not the case, since a parent and children are often typed together. But near relatives should be included in a random sample no more frequently than the fraction they form of the population studied. Thus, if close relatives (the parents, siblings, and children) of the average individual were to represent, say, 0.1 per cent of the population, then close relatives should constitute only 0.1 per cent of the sample. There are, to be sure, methods whereby relatives

may be included in estimating the frequencies of *dominant* alleles, but these methods are rather complex and appear not to have been widely used. In any case, they are not applicable to most blood group genes. It is not clear from previous reports whether precautions to exclude near relatives from the samples were taken in either of the reported series. It may be that failure to do this is responsible for the rather considerable differences between the Rh frequencies in Wiener's and Levine's two series.

Although the two small series spoken of were adequate to disclose the unique character of the Rh frequencies in American Negroes, especially the astonishingly high value of the Rh_0 type, it is clear that far more should be done (a) to determine the exact frequencies in the American Negro population of the various Rh types, especially the rarer ones, (b) to discern whether regional differences exist, and (c) to reduce standard errors to the point where the frequencies of the less common types can be compared with those of African Negro peoples and the differences established as significant. It is obvious from mere inspec-

TABLE 2. FREQUENCIES OF THE Rh SUBTYPES AMONG AMERICAN NEGROES

	Rh_0	Rh_1	Rh_2	Rh_{12}	rh	rh′	rh″	rh‴	TOTAL
Baltimore (Rh Lab.)	397	234	140	57	65	13	—	1	907
Percentages	43.8	25.8	15.4	6.3	7.2	1.4	—	0.1	
New York City (Wiener)	93	45	50	12	18	5	—	—	223
Percentages	41.7	20.2	22.4	5.4	8.1	2.2	—	—	
New York City (Levine)	62	32	22	6	10	2	1	—	135
Percentages	45.93	23.7	16.3	4.44	7.41	1.48	0.74	—	

tion that the statistical errors of estimation are often so large as to render invalid many of the comparisons between ethnic groups.

At the Baltimore Rh Typing Laboratory, for the reasons given, we have undertaken to determine the Rh types of a sufficiently large sample of the local Negro population. In order to assure a strictly random sample of this population the typings of adult individuals involved in legal suits respecting paternity were used, with the precaution that no individual was included in the series twice and that no sibs or other immediate relatives were included. A total of 907 individuals has been typed to Dec. 5, 1951, with the results shown in Table 2. A comparison of these frequencies with those obtained by Wiener, Belkin, and Sonn and by Levine shows a very close agreement between Levine's series and the Baltimore series ($\chi^2 = 1.381$; D.F., 5; P = .90–.95). The agreement of the Baltimore series with Wiener's series is not so close, although still not significantly different ($\chi^2 = 8.713$; D.F., 5; P = .10–.20). Most of the difference lies in the values for type Rh_2 (cDE), although some difference in

the frequency of Rh_1 (CDe) is also manifest. On the basis of the Baltimore series, confirmed by that of Levine, Wiener's frequency for Rh_2 is somewhat too

TABLE 3. Rh GENE FREQUENCIES

	AFRICAN NEGRO		N. AMERICAN NEGRO[4]	U.S. AMERICAN WHITE[5]
R^o (*cDe*)	Ewe[1]	.547	.446	.028
	E. Afr.[2]	.63		
	S. Afr. Bantu[3]	.633		
R^1 (*CDe*)	Ewe	.077 (?)	.145	.420
	E. Afr.	.05		
	Bantu	.047		
R^2 (*cDE*)	Ewe	.035 (?)	.101	.151
	E. Afr.	.075		
	Bantu	.060		
R^z (*CDE*)	Bantu	.016	.015	
r (*cde*)	Ewe	.238 (?)	.268	.383 (.365)
	E. Afr.	.230		
	Bantu	.189		
r' (*Cde*)	Bantu	.054	.025	.014
r'' (*cdE*)	Bantu	.001	.000	.008 (.003)
r^y (*CdE*)	Bantu	.000	.000	

[1] Armattoe, 1950.
[2] Donegani, Ibrahim, Ikin and Mourant, 1950.
[3] Shapiro, 1951.
[4] Baltimore Rh Typing Laboratory, this paper.
[5] Unger, Weinberg, and Lefkon, 1946.

Gene frequency formulae (Wiener, 1943)

$$r = \sqrt{rh}$$
$$r' = \sqrt{rh' + rh} - \sqrt{rh}$$
$$r'' = \sqrt{rh'' + rh} - \sqrt{rh}$$
$$r^y = \text{negligible}$$
$$R^o = \sqrt{Rh_o + rh} - \sqrt{rh}$$
$$R^1 = \sqrt{Rh_1 + Rh_o + rh' + rh} - \sqrt{rh' + rh} - \sqrt{Rh_o + rh} + \sqrt{rh}$$
$$R^2 = \sqrt{Rh_2 + Rh_o + rh'' + rh} - \sqrt{rh'' + rh} - \sqrt{Rh_o + rh} + \sqrt{rh}$$
$$R^z = 1.00 - (R^o + R^1 + R^2 + r + r' + r'')$$

high and that for Rh_1 too low. In the present study the values obtained in the Baltimore series will be used. Table 3 gives the respective Rh allele frequencies.

It also appeared worthwhile to use the individuals in the Baltimore random sample in order to obtain a further check on the frequencies of the MN types and the subgroups of the ABO system in American Negroes. Information was available for 605 persons regarding their ABO subgroups, and for 580 as regards their MN types. Tables 4 and 5 present the results, in comparison with those available from other studies. From Table 4 it is apparent that the allele frequencies determined by Snyder for U. S. Negroes, mostly from N. Carolina, agree almost exactly with those in the present series from Baltimore. The data from New York City diverge somewhat more widely, yet not to a significant extent. On the other hand, the gene frequencies of the ABO blood group system seem to vary more among the African Negroes than either the Rh or MN gene frequencies (Tables 3 and 5, respectively). This agrees with a recent statement

TABLE 4. FREQUENCIES OF ABO BLOOD TYPES

	NO.	A	B	AB	O	GENE FREQUENCIES		
						$p(I^A)$	$q(I^B)$	$r(I^O)$
W. African Negroes								
Yoruba(?)[1]	325	21.5%	23.0%	3.2%	52.3%	.133	.143	.724
Sierra Leone[2]	635	25.0%	24.1%	3.5%	47.4%	.163	.157	.689
Fr. Guinea[3]	200	28.5%	24.0%	4.0%	43.5%	.189	.163	.659
Senegalese[4]	238	21.0%	29.8%	3.0%	46.2%	.140	.192	.680
Ewe[5]	853	20.4%	29.3%	7.4%	42.9%	.142	.196	.662
Aver.	2,251					.153	.174	.673
N. American Negroes								
Baltimore[6]	605	171 (28.3%)	121 (20.0%)	25 (4.1%)	288 (47.6%)	.180	.132	.688
N. Carolina[7]	500	140 (28.0%)	100 (20.0%)	25 (5.0%)	235 (47.0%)	.181	.134	.685
New York[8]	730	221 (30.3%)	159 (21.8%)	27 (3.7%)	323 (44.2%)	.198	.148	.665
N. American Whites								
New York City and N. Car.[9]	30,000	11,840 (39.5%)	3,350 (11.2%)	1,250 (4.2%)	13,560 (45.2%)	.248	.078	.674

[1] Lewis and Henderson (W); Muller (B).
[2] Julien (B).
[3] Chaigneau, Chauzy, and Guerriers (B).
[4] Hirszfeld and Hirszfeld (B).
[5] Armattoe, 1950.
[6] Baltimore Rh Typing Laboratory, this paper.
[7] Snyder (W; B).
[8] Landsteiner and Levine (W; B).
[9] Tiber, Snyder (W; B)

W = Wiener, 1943; B = Boyd, 1939

by A. E. Mourant (personal communication, Feb. 21, 1952), who says, in reference to unpublished studies of the blood groups of native Africans made by himself and his colleagues, as well as published studies by others: "The most striking fact is the high degree of uniformity in the distribution of the Rh and MNS groups throughout tropical Africa."

One curious anomaly shows up in the data on the MN blood groups among the 580 individuals in the Baltimore sample. Although these individuals are included in the 605 typed for ABO and the 907 typed for Rh, and in spite of the good agreement in the ABO and Rh frequencies with previous published series, there is a notable shortage of type M and an excess of type N in the present series. The situation will require further investigation. However, it is not of consequence in the present analysis, inasmuch as the MN blood groups

are not usable anyway, since the difference in the MN allele frequencies of African Negroes and U. S. Whites is too small to permit an accurate estimation of gene flow.

Usable data exist, however, for the alleles that determine the capacity, or lack of capacity, to taste phenylthiocarbamide (P.T.C.). These are presented in Table 6.

If the several traits considered are now arranged according to descending order of magnitude of the interval between the allele frequency in the W.

TABLE 5. FREQUENCIES OF MN BLOOD TYPES

PLACE	NO.	M	MN	N	GENE FREQUENCIES	
					p (L^M)	q (L^N)
African Negroes						
S. African Bantu[1]	505	135 (26.8%)	255 (50.5%)	110 (21.8%)	.5205	.4705
Ewe[2]	853	243 (28.48%)	490 (57.48%)	120 (14.04%)	.572	.428
N. American Negroes						
Baltimore[3]	580	136 (23.45%)	280 (48.25%)	164 (28.3%)	.476	.524
New York City[4]	278	(28.42%)	(49.64%)	(21.94%)	.532	.468
Michigan[5]	96	28 (29.25%)	43 (44.75%)	25 (26.0%)	.516	.484
N. American Whites						
New York[6]	6,129	1,788 (29.16%)	3,040 (49.58%)	1,305 (21.26%)	.550	.450

[1] Shapiro, 1951.
[2] Armattoe, 1950.
[3] Baltimore Rh Typing Laboratory, this paper.
[4] Combined data of Landsteiner and Levine, and Wiener (from Wiener, 1943).
[5] Neel and Hanig, 1951.
[6] Combined data of Landsteiner and Levine, Wiener, Herman and Derby, and Hyman (from Wiener, 1943).

African population and that in the U. S. White population, the following series is obtained: (Secondary or less reliable estimates in parentheses.)

R^0	.602	(.519)
R^1	.370	
T/t	.340	(.381)
r	.153	(.078)
I^B	.096	(.118)
I^A	.095	(.106)
R^2	.076	
L^M	.0295	(.022)
L^N	.0205	(.022)
I^O	.001	(.012)

For the first seven genes the interval is of sufficient magnitude to make an estimate of gene flow possible, although of course the relative magnitude (a) of errors of estimation of the allele frequencies and (b) of uncertainty due to the differences between the tribes and subpopulations sampled become correspondingly greater as the interval decreases. Hence the most reliable estimates of gene flow will be derived from the three genes at the top of the list, with R^o considerably better than any other.

THE STATISTICAL MODEL

Since the hybrid individuals between Whites and Negroes are in the United States regarded socially as Negroes, any interbreeding between the two populations will result chiefly in a "one-way" gene flow from the White to the Negro population. The reverse process of "passing" is mostly a comparatively

TABLE 6. FREQUENCIES OF PHENYLTHIOCARBAMIDE TASTE CAPACITY

	TOTAL	PTC+	PTC−	GENE FREQUENCIES	
				T	t
African Negroes					
Sudan[1]	805	771 (95.8%)	34 (4.2%)	.795	.205
E. Africa[1]	110	101 (91.82%)	9 (8.18%)	.714	.286
75% W. Africa, 25% E. Africa[2]	74	72 (97.28%)	2 (2.72%)	.835	.165
N. American Negroes					
Ohio and "southern"[1]	3,156	2,865 (90.78%)	291 (9.22%)	.697	.305
N. American Whites					
Ohio[3]	3,643	2,556 (70.16%)	1,087 (29.84%)	.455	.545

[1] Lee, 1934.
[2] Barnicot, 1950.
[3] Snyder, 1932.

recent one, and the number of people who have crossed the color line is but a small fraction of the white population as a whole. This is shown by the fact that the Rh_0 frequency of the American White population is not significantly different from that of Western Europe (see Table 1). The effect of "passing" on the gene frequencies of the American Negro and White populations is therefore ignored in the following model.

Let q_0 be the original allele frequency of the Negro population prior to any interbreeding with the whites; and let Q denote the frequency of the same allele among the American whites and assume that it has been constant throughout the last two or three centuries, since it is not affected by the interbreeding between Whites and Negroes. Now, let m be the fraction of the Negro gene pool which is derived from Whites in each generation, or, more precisely, the fraction of the Negro genes that has been replaced by the immigrated White

genes through interbreeding in each generation. Then, after the first generation of interbreeding, the allele frequency of the resulting Negro population will be changed from q_0 to

$$q_1 = (1 - m)\, q_0 + mQ. \tag{1}$$

For the sake of simplicity, let us assume that the value of m remains constant from generation to generation, although in reality it might be increasing, decreasing, or both successively. Then, after two generations of interbreeding with the Whites, the Negro allele frequency will be

$$q_2 = (1 - m)\, q_1 + mQ, \text{ etc.}$$

If the process continues for k generations, the Negro allele frequency will be

$$q_k = (1 - m)\, q_{k-1} + mQ.$$

By successive substitutions of $q_{k-1}, q_{k-2}, \cdots, q_2, q_1$, we obtain

$$q^k = (1 - m)^k q_0 + mQ + (1 - m)mQ + \ldots + (1 - m)^{k-1} mQ.$$

The last k terms on the righthand side of the above equation form a geometric series whose sum is

$$mQ \left\{ \frac{1 - (1-m)^k}{1 - (1-m)} \right\} = \left\{ 1 - (1 - m)^k \right\} Q.$$

Hence, the general expression for the Negro allele frequency after k generations of interbreeding with the Whites is

$$q_k - (1 - m)^k\, q_0 + \{1 - (1 - m)\}^k\, Q. \tag{2}$$

If the original and present American Negro allele frequencies as well as that of the American Whites have been determined and we are interested in finding the values of m and k which would account for the observed results, the above equation (2) may be written in a more convenient form:

$$(1 - m)^k = \frac{q_k - Q}{q_0 - Q} \tag{3}$$

Substituting the numerical values of q_0, q_k, and Q, the value of m may be obtained under any assigned value of k. The results presented in the following section are all calculated by this formula (3). Under each pair of values of k and m, the successive allele frequencies of the changing Negro population in these k generations may be calculated by repeated application of (1). Alternatively, we may notice that the amount of change in Negro allele frequency in any generation is

$$\Delta q_k = q_{k+1} - q_k = - m(q_k - Q) \tag{4}$$

the repeated application of which would also give us the successive allele frequencies of the Negroes.

It is evident that the larger the value of k, the smaller the value of m. In some of the following numerical tables, it may be noted that the product mk is approximately constant, that is to say, m is approximately inversely proportional to k, provided that m is small and k large, in which case the equation (4) may be regarded as a differential equation by writing $\Delta q = dq/dt$, where t denotes time in units of generations. Separating the variables and integrating both sides within the appropriate limits, we have

$$\int_{q_0}^{q_k} \frac{dq}{q - Q} = -m \int_0^k dt$$

$$\log_e (q - Q)]_{q_0}^{q_k} = -mk$$

$$\frac{q_k - Q}{q_0 - Q} = e^{-mk}$$

which is an approximation form of our previous equation (3) for small m and large k. Since the values of q_0, q_k, and Q are observed, the value of mk may be determined. In the following tables, however, the more accurate form (3) has been used to calculate the values of m.

ESTIMATION OF THE NUMBER OF GENERATIONS OF INTERMIXTURE

From the equation given, it is evident that the estimate of m, the gene flow, will depend upon the estimate of k, the number of generations of intermixture. This in turn will depend upon the length in years of the period throughout which intermixture has occurred, and the average length in years of a generation.

The length of period is fairly accurately determinable. The first shipload of Negro slaves was brought to the North American colonies in 1619. Virginia, which obtained the majority of the early supply of slaves, had 300 in 1650 and 2000 by 1671. It is stated that by 1720 one-seventh of the population of New York, one-thirteenth of that of Pennsylvania, one-half that of Maryland, one-third that of North Carolina, and over one-half in Virginia and South Carolina consisted of slaves. The total was close to 75,000. It seems probable that the earliest shiploads consisted entirely of male slaves, and the beginning of the period of intermixture can as a consequence scarcely be set before 1650. Perhaps 1675 would be a better choice as a date for the beginning of appreciable intermixture. Certainly it must have been well under way by 1700. The period is thus one of 275 years (1675–1950) or possibly 300 years.

The length of generation at the present time may be determined with sufficient accuracy from the *Vital Statistics of the United States, 1948* (Part II, Table 8, p. 168). The average age of non-white mothers at the births of their children is given as 25 years; of non-white fathers at the births of their children

as 30 years. These individuals must have been predominantly Negroes. The average age of Negro parents at the births of all children is thus 27.5 years. A more refined method could be used (see Dublin and Lotka, 1925), but the result is not appreciably different, according to Dublin (personal communication, March 11, 1952).

Undoubtedly the average length of generation has not been constant for the N. American Negro population. There are several reasons why it was most likely shorter in the past. In the first place, mortality rates were considerably higher than now and average length of life correspondingly less. Particularly under slavery, the hard life of labor experienced by many slaves must have cut short their reproductive period. Secondly, the prevalence of venereal disease, especially gonorrhea, must also have shortened the reproductive period of the females. Thirdly, there has been a more recent tendency for the U. S. Negro population to imitate the social pattern of the U. S. Whites in postponing marriage and childbearing to later years. This is seen in the fact that the average length of generation at the present time is not very different for the two populations, namely, 27.5 years for the U. S. Negroes and 28 years for the U. S. Whites. To be sure, the average Negro primipara is considerably younger than the average White primipara, but this is counterbalanced by a longer period of childbearing, so that the age of parents at the birth of the median child, which is the statistic of importance in calculating the average length of generation, comes out almost the same for Negroes and Whites.

From the three reasons given above, it appears reasonably certain that if the figure of 27.5 years for the average length of generation in the U. S. Negro be taken, the estimated number of generations in the period since 1675 will be a *minimum* estimate. This is important for the following reason. The change of m with changing k is great when k is low but becomes less and less as k increases. This is to be seen from the estimates of m for various values of k determined from the R^o gene frequencies (see Table 7). In Fig. 1 the relation is represented graphically. It may be seen that up to 7 or 8 generations, the change in m per unit change of k is rapid, but by the tenth generation the slope of the curve is much more gradual, and thereafter it flattens out more and more. Hence, if the estimate of k as 10 generations is a minimal estimate, increase in the real number of generations to 12 or 13 makes only a slight difference in the estimated value of m. In fact, the error from underestimation of k is thus reduced to a magnitude no greater than the errors of estimate due to choice of a particular W. African population as the base population or to many of the sampling errors.

ESTIMATION OF THE GENE FLOW

Table 7 gives the calculated values of m for various values of k, when the estimate is based on the R^o data. If we take 10 generations as a reasonable

estimate for the period of intermixture, then the accumulated amount of white admixture is 30.565 per cent, and m, the average rate of gene flow from the U. S. White population into the U. S. Negro population, is estimated to be 3.58 per cent per generation. This percentage is a percentage of the U. S. Negro

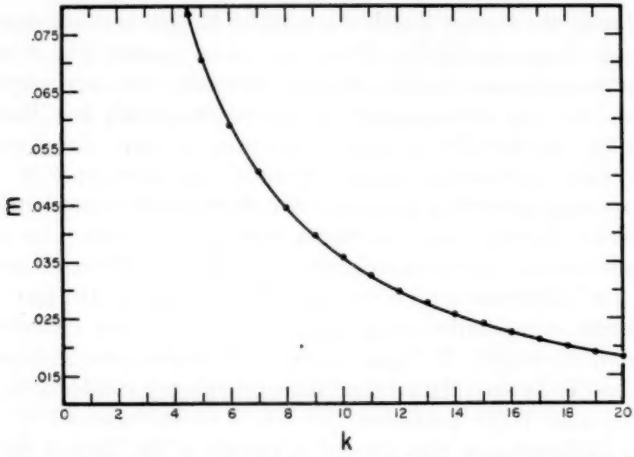

FIG. 1. Change in the estimate of the gene flow (m) with variation in the number of generations (k) of intermixture, when $(1 - m)^k = .69435$. From the curve it is apparent that for relatively short periods of intermixture ($k < 8$) the change in the estimate of m per unit change in k is considerable. When k is 10 generations or more, the change of m per unit change in k is small. Hence follows the importance of making a *minimum* estimate of k.

TABLE 7. THE VALUES OF k AND m AS DETERMINED BY R^o GENE FREQUENCIES (See Table 8)

k	m	k	m
1	0.3057	11	0.0326
2	.1667	12	.0299
3	.1145	13	.0277
4	.0872	14	.0257
5	.0704	15	.0240
6	.0590	16	.0225
7	.0508	17	.0212
8	.0446	18	.0200
9	.0397	19	.0190
10	.0358	20	.0182

population at each generation, and thus renders the estimate free of influence from any increase in the size of the U. S. Negro population, any change in its relative size in comparison with the U. S. White population, and any influx of pure Negroes from Africa during the period of intermixture.

Table 8 presents the estimates of m from the seven different sets of allele frequencies available. Agreement is striking, and well within the limits of

error of estimation. More reliable estimates must await more extensive knowledge of the blood group frequencies in West Africa, as well as more accurate determinations in U. S. Negroes and Whites. The existence of heterogeneity among the U. S. Negroes in different regions of the country has not been ade-

TABLE 8. THE AVERAGE RATE OF GENE FLOW FROM THE U. S. WHITE INTO THE U. S. NEGRO POPULATION DURING THE PERIOD OF INTERMIXTURE

(assuming $k = 10$)

GENE	q_0		q_k	Q	m
R^o	E. Afr.	.630	.446	.028	**.0358**
	Bantu	.633			.0363
	Ewe	.593(?)			(.0297)
R^1	E. Afr.	.05	.145	.420	**.029**
	Bantu	.047			.030
	Ewe	.077(?)			.022(?)
T/t	Sudan	.205	.303	.545	**.0334**
	Barnicot	.164			.044
r	E. Afr.	.230	.268	.383	**.028**
	Bantu	.189			.051
	Ewe	.238(?)			(.023)
I^B	Aver.	.174	.132	.078	**.056**
	Yoruba	.143			.018
	Sierra Leone	.157			.037
	Ewe	.196			.075
I^A	Aver.	.153	.180	.248	**.033**
	Yoruba	.143			.043
	Sierra Leone	.163			.022
	Ewe	.142			.043
R^2	Bantu	.060	.101	.151	.058
	E. Afr.	.075			**.041**
	Ewe	.035			(.081)

Values of m regarded as most reliable are in heavy numerals. Those of considerable uncertainty (Ewe) are placed in parentheses.

quately investigated either, and has an important bearing on these determinations.

The three most reliable estimates agree within a range of .0068. Although the estimate derived from R^o is the highest of these three, it is also the most reliable estimate, and can be accepted provisionally until further evidence is available, as being the rate of gene flow from the U. S. White into the U. S. Negro population.

DISCUSSION

It is obvious that the estimated rate of gene flow per generation need not have been constant. In fact, if the rate of introgression of genes from the White population was much greater in the past than today, the present rate may be considerably less than .0358. The advantage of expressing the intermixture in the form of a rate rather than simply as a given amount of admixture is that the present rate may conceivably be measurable. In that case it will become possible to say definitely whether the rate of admixture was greater under slavery, i.e., before the Civil War, and since then has diminished, or whether on the contrary it has increased beyond earlier rates. Clearly, the length of

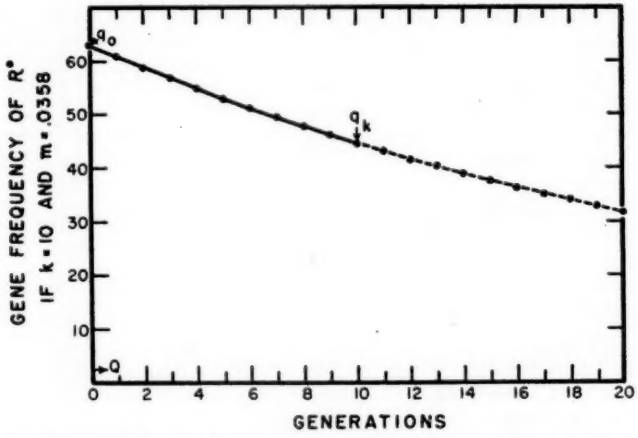

FIG. 2. The change in allele frequency of R^0 in the North American Negro population from q_0 = .63 to the present (q_k = .445) over 10 generations, assuming constancy in the rate of change. The dotted line is the extrapolation of the curve, assuming constancy in the rate of gene flow, for the next 10 generations. Q, the frequency of the R^0 allele in the North American White population today.

time that must pass before the American Negro becomes indistinguishable genetically from the remainder of the U. S. population will depend upon whether the rate accelerates, remains constant, or slows down. Very much speculation has been indulged in on this subject by sociologists and others, but apparently without any serious, objective grounds for their opinions.

Table 10 presents a sample extrapolation for different values of m of the number of generations needed to reduce the frequency of the R^0 allele in the American Negro population from its present value to a value one-tenth of the original frequency, that which is found in the African Negro. It happens that this frequency is very close to that which will obtain at equilibrium in the combined population if the respective elements retain their present proportions of 11 per cent and 89 per cent. This equilibrium frequency is .074, and

it would be reached in 60.7 generations, or 1669 years, if m were to remain at .0358 and k at 27.5 years.

It is of course highly improbable that the rate of intermixture will remain constant, and also quite unlikely that the length of generation will stay unchanged; but, in the absence of specific evidence to indicate how these conditions will change, the extrapolation into the future on the basis of the average

TABLE 9. THE SUCCESSIVE VALUES OF R^0 GENE FREQUENCIES IN THE AMERICAN NEGRO POPULATION UNDER SPECIFIED NUMBERS OF GENERATIONS OF INTERBREEDING

GENERATIONS OF INTERBREEDING	$k = 8$ $m = 0.0446$	$k = 10$ $m = 0.0358$	$k = 12$ $m = 0.0299$
0	0.6300	0.6300	0.6300
1	.6032	.6084	.6120
2	.5775	.5877	.5945
3	.5530	.5676	.5776
4	.5296	.5483	.5612
5	.5072	.5297	.5452
6	.4858	.5117	.5298
7	.4654	.4944	.5148
8	0.4460	.4777	.5002
9		.4616	.4861
10		0.4460	.4724
11			.4591
12			0.4461

TABLE 10

GENE FLOW PER GENERATION, m	NEEDED TO REDUCE R^0 GENE FREQUENCY FROM .446 TO 0.063 IN AMERICAN NEGROES	
	Number of generations	Years, at 27.5 yrs. per generation
%		
6.0	40.1	1103
5.5	43.8	1205
5.0	48.3	1328
4.5	53.9	1480
4.0	60.7	1669
3.5	69.6	1914
3.0	81.4	2238
2.5	97.9	2692
2.0	122.8	3377

rate that has prevailed over the past three centuries and the present length of generation is better than a mere guess. The length of period required may seem surprising in view of the high rate of racial intermixture which has prevailed; but that is the necessary consequence of the logarithmic type of change shown in the equation, in contrast to a simple linear rate of admixture.

Certain factors, however, may shorten the required span of time. First is

the fact that complete equilibrium need not be attained before the distinction between the two populations may become indistinguishable to ordinary observation. If, for example, the ordinarily distinguishable limit is taken to be a difference of the allele frequencies amounting to 10 per cent of the original difference, then the limit would be attained in about 39 generations or between 10 and 11 centuries (1072.5 years). This is only two-thirds of the time required for complete equilibrium. It should be noted that these estimates apply to any and all genes, since they depend only on the determined values of m and k, and not upon particular gene frequencies. The prediction, crude as it is, thus applies to all distinguishing racial, hereditary characteristics. Secondly, it seems probable that the rate of gene flow will tend to increase as the limit of distinguishability of the two groups by ordinary observation is approached. In other words, m should increase as the equilibrium is neared. In the third place, gene flow in the opposite direction should eventually become discernible, in spite of the much larger size of the U. S. White population, and will contribute its share to the attainment of the equilibrium. The latter may therefore be reached considerably sooner than the prediction on the basis of constant m and k. The predicted time of attainment of complete assimilation may therefore be regarded as an upper limit, provided there has not been a decided decrease in m since the end of slavery.

At any given time a population will contain individuals sufficiently different in age to cover three generations. It is consequently to be expected that different allele frequencies will be found in successive generations. This is a phenomenon which has been given little or no consideration in gene frequency analyses of human populations. If a population is not in equilibrium, however, the gene frequency analysis should separate different age groups, and the analysis of successive generations should yield data of considerable interest. In the present case, if m has remained constant, we would expect a change per generation (Δq, Equation 4) of .015 in the R^o allele frequency. This is of course a very small change, but accumulated over two generations, and thus amounting to a change of approximately .03, the sampling variance would permit it to be detected in samples of about 1200 persons each from the oldest and youngest generations, respectively. If the rate of intermixture in earlier times was greater than now, then the expected change would be less than .015 per generation; and conversely, if the rate has increased since the end of slavery, the change to be expected would be greater than .015 per generation. Obviously, the question whether the rate of change is significantly greater than $m = .0358$, or whether it is less, could only be determined in much greater samples. In this case it would be much more practical to let the change accumulate over more than two intervals between generations; but at least the ascertainment of the allele frequencies which exist in the generations now living will provide a basis for the continuation of such analysis in the future.

Unless the rate of gene flow between populations is extremely high, the dynamics of racial intermixture can be studied only over a suitably long period, like other aspects of population change.

The proposed determination of the allele frequencies in successive generations, and the comparison of the rate of change with that to be expected on the basis of the rate of change in the past, of course assume that no factors will operate selectively on different genotypes in such a way to to change the frequencies among older people from those characteristic of the young. Detection of age changes in allele frequencies would in itself be of great interest, and might serve to establish the selection characteristics of various traits. Even more significant may be the detection of changes in the frequencies of the several genotypes. Evidence has been accumulating that polymorphism in populations often involves a selective advantage of the heterozygote over both types of homozygote. This ought to become apparent in a comparison of genotype frequencies in the youngest generation with those in the oldest. Perhaps only in this way can the question be clarified whether the polymorphism of the human species in its various systems of blood types has selective significance. In the present context, however, the solution of this problem does not seem too simple. Superimposed upon the age changes in gene and genotype frequencies due to selection are those due to gene flow between populations. These may often be of greater magnitude than the former. Those who are working with the population analysis of such hereditary traits as thalassemia and sickle cell anemia will therefore need to take the necessary precautions to distinguish between the change in gene and genotype frequency in young versus old individuals which is due to selection from that which is likely to be present in any population, of mixed origin or not, that is undergoing genetic intermixture with other populations.

A change in allele frequencies in successive generations of a population, especially if it is opposed in direction to the obvious action of selection, will serve to show whether or not the population is in genetic equilibrium. Thus, in the case of sickle cell anemia, persons of an older generation would be expected, because of selection, to show a lower frequency of the allele for sickling than persons of a younger generation. But in the United States the allele for sickling is almost entirely confined to the American Negro population, so that the effect of racial intermixture will reduce the frequency of the sickling allele in successive generations. It will be interesting to see whether in this case the effect of selection or the effect of the racial intermixture predominates.

From what has been said, it is obvious that the accumulated change in allele frequency seen in such a mixed population as that of the American Negro may not be wholly attributable to gene flow. Genes introduced into the American Negro population over k generations have been subjected to the action of selection since the date of their introduction. The accumulated change

is therefore that due to the combined effects of gene flow and selection. Nor can it be safely assumed that selection will continue to act on the competing alleles in the New World and under the conditions first of slavery and then of emancipation as it acted upon them in the Old World, especially since the breakup of coadapted genotypes, inevitable in a population undergoing intermixture, might lead to considerable alterations in the selective value of particular alleles. In the absence of evidence, nothing definite can be stated about the extent to which selection has modified the frequencies in the American Negro population of those alleles used in the present study. However, certain indications that it is not very important may be pointed out. In the first place, because in all three populations Rh alleles with *d* are less frequent than those with *D*, selection because of maternal-fetal incompatibility would be expected to decrease the former and increase the latter (Wiener, 1942; Haldane, 1942; Glass, 1950). *r*, the allele with the great majority of *d*, should then in all cases become rarer. But the actual event is the contrary. In the American Negro population *r* is becoming commoner, against the pressure of selection, that is, in spite of the resulting increase in frequency of hemolytic disease of the fetus and newborn. Moreover, the value of *m* calculated from *r* frequencies is no different from that calculated from the R^1 frequencies, although the latter allele is presumably favored by selection.

In general, it may be suggested that when a sufficiently large number of genes is considered, it is unlikely that in the hybrid population all alleles at all loci will be shifted by selection in the direction of those frequencies characteristic of a particular base population, rather than some toward the one and some toward the other. To assume the former is to assume in the favored base population (here the U. S. White) a degree of adaptation to environment and of coadaptation of genotype that is scarcely compatible with what we know of the rapidly changing conditions of life and the evanescence of particular gene combinations in the outbreeding, migrating human populations of modern times. Although the authors therefore lean toward the view that selection has not significantly obscured the relation of allele frequency in the American Negro population to gene flow, for those alleles involved in the present study, these questions clearly suggest lines of profitable investigation for the future.

SUMMARY

1. A method is given whereby the dynamics of population intermixture may be studied. The gene flow per generation from one base population into a hybrid population, as in the example of the introgression of genes from the U. S. White population into the American Negro population, is given by the equation $(1 - m)^k = (q_k - Q/q_0 - Q)$, where k is the number of generations of intermixture, q_k is the allele frequency at a given locus in the hybrid population, q_0 and Q are the frequencies of the same allele in the two base populations,

and m is the percentage of genes in the mixed population which are introduced per generation from the population with allele frequency Q. From the data for the R^o allele, the accumulated amount of white admixture in the N. American Negro is estimated to be 30.565 per cent.

2. The method has been applied to estimate the average amount of gene flow per generation from the U. S. White population into the American Negro population. Seven sets of allele frequencies (R^o, R^1, T/t, r, I^B, I^A, and R^2) were found suitable for independent determinations of the value of m. The estimates of m obtained showed good agreement. The most reliable, that for R^o, is $m = .0358$, on the assumption that there have been 10 generations of intermixture.

3. A method of investigating alterations in the value of m in the course of time is outlined. It is based on the detection of changes in allele frequency accumulating in the course of two or more successive generations in a population undergoing genic introgression.

4. New data on the frequencies of the Rh, ABO, and MN blood groups in American Negroes have been used in the present study. It is believed that the individuals typed represent, in so far as blood groups are concerned, a truly random sample of the Baltimore Negro population. The frequencies obtained differ, but not greatly, from those previously published. They represent the largest series yet reported for Rh and MN. However, the MN series is anomalous in that a higher frequency of N than of M was found.

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Seasonal Variation in the American Live Birth Sex Ratio

HERMAN M. SLATIS

Department of Genetics, McGill University, Montreal 2, Quebec

INTRODUCTION

It is important for human geneticists to know the extent of the influence of the external environment on genetically determined characters in man. For traits which are visible at birth, the action of the environment may be either to affect the phenotype (penetrance, expressivity), or to affect the frequency of occurrence of the character by eliminating it differentially during gestation. The changing seasons are the environmental factors most likely to produce enough of an effect on man's physiology to be observable. Data are available for the study of seasonal variation in the incidence of one particular character for which the genetic mechanism is understood: sex. Although statistically it is most easy to work with the proportion of males (or females) at birth, most of the literature is in terms of the number of males per hundred females. The proportion of males at birth is known as the secondary sex ratio.

A few investigators have claimed the finding of a seasonal variation in the sex ratio among live births. Huntington (1938) noted a low male/female ratio in February and March, a high ratio in the summer, and little deviation from average during the last part of the year. His values are based on the compilation of data from various parts of the world and contain striking departures from the average. There is reason to believe that some of his data are unreliable. The same year, Ciocco (1938), after an examination of the data for the United States for the period from 1925 through 1934, concluded that the influence of the seasons on the sex ratio is negligible or absent. Strandskov (1942), using a delicate statistical test, failed to find monthly variation greater than might be attributed to chance in the United States data for the year 1935. Orwig (1948), in an analysis of the sex ratio in the United States for the years 1922 through 1936, found significant variation among the months. A graph which is included in his paper shows a rise in the proportion of male live births each month from February to June, followed by a drop each month from then to December. January is exceptional on this graph as it shows a proportion of males which is exceeded only during May, June, and July. Orwig confined his report to the statistical significance of the monthly variations. He did not discuss the apparent seasonal variation.

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DATA

To look for seasonal fluctuations in the American live birth sex ratio, the pertinent data compiled by the United States Bureau of the Census have been utilized. At present, these data are collected over the entire country. In the past, records have not been published for particular years, and the inauguration of the collection of records has varied among the states. The first year for which data from each state are included in this paper is indicated in table A in Birth, Stillbirth, and Infant Mortality Statistics for the Birth Registration Area of the United States (1936). Publication of the number of live births by sex and by month for ten states and the District of Columbia was begun in 1915 in the annual Birth Statistics for the Registration Area of the United States (1915–1921). This was continued in the annual Birth, Stillbirth, and Infant Mortality Statistics for the Birth Registration Area of the United States (1922–1936). From 1915 to 1930, these publications listed the number of live births by sex and by month in each state (for which data were available) and often for each registration area within each state. The individual registration areas were combined into urban and rural groups. During this period the United States Registration Area was increasing in size, and in 1931, when all but two states were reporting, the publication of this detailed analysis was dropped. From 1931 to 1936, the only data listed by sex and month of birth were national totals for urban areas (cities of 10,000 and over), cities of 2,500 to 10,000, rural areas, and the registration area as a whole (which has included the entire nation since 1933). No records pertinent to this analysis are available for the years 1937 to 1941. Since 1942, the annual Vital Statistics of the United States, Part II, has included data on the number of live births by sex and by month for each state and separately for the white and nonwhite races within each state. Publication of birth records is delayed by several years. Accordingly, 1948 is the last year for which data are included in this paper.

The first row of table 1 lists the totals for all published data. Below this row the same data are broken down into three periods of years, the grouping being determined by the manner in which the data were issued by the Bureau of the Census. This is followed by a division into nine geographical regions, with separate listings for the years 1915–1930 and 1942–1948. In general, the states have not shown features of interest, and usually the number of births is small. For these reasons, the states will not be discussed individually, although the data for each have been examined separately. These data have been compiled for this paper into geographical regions. Tables illustrating the allocation of the states to these regions may be found in Vital Statistics of the United States, Part I (1948). The next data in table 1 are those which are reported by race. Although listed as "white" and "nonwhite", about 95% of the latter category consists of Negroes. Except in the south, the nonwhite population is not large enough to warrant comparison with the whites in the same area, so that only

the South Atlantic and the South Central regions are given by race (in the latter case by pooling the data for the East and West areas). The last grouping in table 1 lists data for various urban and rural areas.

Throughout this paper, proportions of male births are expressed as deviations from the overall average for the area and the years involved. The unit in which these deviations are given has been taken as .001 of the percentage of live born males. For example, in the first row of table 1 the January value for the U. S. Registration Area for 1915–1948 is 37 (.001% units). This should be added to the average proportion of males born during these years, 51.367%, to give 51.404% male births in January. On the other hand, February 1915–1948 has a value of −139 (.001% units), which, subtracted from the value of 51.367%, gives 51.228% male births. This method of representing the differences as fluctuations about their own mean has been employed because the observed proportion of male births may be unreliable in magnitude. The figures have been compiled in table 1. Shown are the total number of live births in the component reported, the first and last years included in the period, the average percentage of male births for the total period, and the monthly deviations from this in units of .001% (these deviations will usually not total zero because monthly variations in the number of live births are not random with respect to the variation in the sex ratio). Figures for years prior to 1933 are only for those states within the Birth Registration Area at that time, so periods beginning with 1915 or 1930 must be understood merely as designating all available data within that group of years.

The significance of the difference between any two figures in the same row in table 1 may be determined by reference to table 2. This table has been prepared by assuming a binomial distribution of sex at birth (neglecting factors such as identical twinning, which fail to conform to this assumption). By choosing a binomial where q is the percentage of males, the standard error of q may be determined for any population of size N by use of the formula

$$100\sqrt{\frac{q(1-q)}{N}}.$$

The formula for the difference between two percentages is

$$\frac{q_1 - q_2}{\sqrt{\text{S.E.}_{q_1}^2 + \text{S.E.}_{q_2}^2}}$$

where q_1 is one percentage and q_2 is the other, and S.E._q^2 is the standard error squared of a percentage as calculated by use of the preceding formula. As all populations in table 1 have roughly 51% males, it is simple to calculate a table showing the value which must be exceeded before a difference between two percentages is statistically significant. For example, a difference of 81 units be-

TABLE 1. MONTHLY VARIATION IN THE LIVE BIRTH SEX RATIO

COMPONENT	YEARS INCLUDED	TOTAL BIRTHS	PERCENTAGE OF MALE BIRTHS	DEVIATION FROM AVERAGE PERCENTAGE OF MALE BIRTHS BY MONTHS IN .001% UNITS											
				Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sep.	Oct.	Nov.	Dec.
U. S. regis. area	1915–48	61,420,640	51.367	37	−139	−69	10	101	113	83	15	5	−65	−55	−42
U. S. regis. area	1915–30	26,887,283	51.395	66	−102	−91	−5	91	116	49	49	−17	−81	−47	−37
U. S. regis. area	1931–36	12,735,565	51.312	39	−167	−69	−53	119	143	145	−62	15	28	−101	−54
U. S. regis. area	1942–48	21,797,792	51.364	0	−171	−41	68	102	90	88	19	25	−98	−38	−41
New England	1915–30	2,637,808	51.316	80	−4	−118	−51	71	164	−137	117	25	−7	−84	−61
New England	1942–48	1,270,610	51.553	−198	191	−59	146	−81	11	169	30	−53	70	−189	−31
Mid. Atlantic	1915–30	7,837,534	51.352	84	−109	−44	68	183	89	89	−24	−11	−117	−73	−154
Mid. Atlantic	1942–48	3,929,691	51.433	−103	−143	15	87	73	138	83	3	53	−215	94	−79
S. Atlantic	1915–30	3,726,766	51.304	−29	−132	42	−82	−52	112	64	90	−56	−37	−27	108
S. Atlantic	1942–48	3,345,497	51.263	−215	−151	−87	42	145	231	2	205	13	−74	−203	102
E. S. Central	1915–30	1,796,621	51.571	256	−178	−264	−69	−26	316	133	102	−43	−226	169	−145
E. S. Central	1942–48	1,969,242	51.391	89	−125	−32	10	115	82	118	0	49	−187	−51	−61
W. S. Central	1915–30	455,359	51.464	319	237	−265	82	−85	−225	76	3	172	−177	−319	118
W. S. Central	1942–48	2,314,118	51.261	139	−394	−193	−53	342	177	105	72	−38	−30	9	−102
E. N. Central	1915–30	6,110,191	51.447	49	−93	−152	45	115	63	−5	132	−31	−15	−32	−86
E. N. Central	1942–48	4,242,702	51.373	188	−270	46	90	154	−106	138	−114	45	−133	−3	−32
W. N. Central	1915–30	2,367,199	51.467	123	25	26	−228	55	140	246	−138	32	−184	−122	9
W. N. Central	1942–48	1,999,367	51.400	39	−271	−39	142	264	−13	43	−20	−7	38	−140	−23
Mountain	1915–30	496,697	51.458	63	−102	−33	−50	58	337	32	−78	2	−287	−199	242
Mountain	1942–48	792,236	51.333	123	−38	−131	−86	−330	218	199	183	155	16	−104	−234
Pacific	1915–30	1,459,108	51.419	−164	−443	−331	119	181	156	−64	152	−75	39	57	360
Pacific	1942–48	1,934,329	51.322	−33	−1	−64	126	−151	178	27	−42	48	−105	95	−67
U. S. white	1942–48	19,200,541	51.462	24	−188	−36	49	94	69	107	56	21	−114	−10	−55
U. S. nonwhite	1942–48	2,597,251	50.635	−128	−21	−63	210	139	230	−57	−101	47	−14	−262	75
S. Atlantic white	1942–48	2,411,063	51.521	−67	−173	−85	56	39	278	96	282	−68	−241	−178	72
S. Atlantic nonwhite	1942–48	934,434	50.598	−555	−68	−67	29	426	109	−250	−13	208	344	−294	180
S. Central white	1942–48	3,320,038	51.512	90	−307	−108	−53	301	28	194	106	−27	−97	30	−147
S. Central nonwhite	1942–48	963,322	50.662	229	−108	−91	128	29	507	−168	−217	60	−187	−245	121

U. S. urban	1915–30	13,540,791	51.360	90	−179	−147	12	94	150	44	101	−8	−26	−14	−128
U. S. rural	1915–30	10,695,780	51.412	73	−33	−32	30	67	80	72	−20	−39	−147	−92	32
U. S. urban	1931–36	5,913,945	51.362	64	−278	8	−2	259	139	168	−39	22	−16	−187	−169
U. S. small cities	1931–36	1,259,964	51.259	−156	−125	−85	−80	−10	114	284	−4	30	23	−8	8
U. S. rural	1931–36	5,561,656	51.270	56	−59	−144	−96	3	153	86	−99	8	76	−29	57
New York City	1915–30	2,097,227	51.277	301	−256	−18	−10	221	156	31	56	−116	−21	29	−418
Other New York urban	1915–30	921,880	51.386	215	−47	16	81	−10	64	220	−332	62	−332	−12	−23
New York rural	1915–30	685,144	51.480	−93	67	21	123	219	189	−44	−237	94	−365	−33	63
Boston	1915–30	305,735	51.235	418	82	−496	−82	264	37	−182	313	77	150	−393	−204
Other New England urban	1915–30	1,630,766	51.336	180	−215	−174	38	−19	249	−96	162	104	−40	−66	−135
New England rural	1915–30	701,307	51.305	−308	452	178	−238	193	25	−210	−73	−178	2	8	179

tween two months is significant at the 1% level for a population of 60,000,000 which is roughly the total number of births analyzed in this paper (first row, table 1). In the total data, the difference between January and February is 37 − (−139), or 176, which greatly exceeds 81, and is, therefore, highly significant.

There are sixty-six different pairs of months. Therefore, sixty-six comparisons may be made in any row of table 1. For this reason, merely because two months differ by a significant amount, one should not accept the difference as real. To accept the difference it must either be highly unlikely on the basis of chance alone, or there must be some other reason.

TABLE 2. LEVELS OF STATISTICAL SIGNIFICANCE BETWEEN TWO MONTHS

TOTAL BIRTHS	AVERAGE NUMBER OF BIRTHS PER MONTH	STANDARD ERROR OF THE AVERAGE MONTH (.001% UNITS)	DIFFERENCE WHICH IS STATISTICALLY SIGNIFICANT (.001% units)	
			5% level	1% level
60,000,000	5,000,000	22	62	81
30,000,000	2,500,000	32	88	115
12,000,000	1,000,000	50	139	182
6,000,000	500,000	71	196	258
3,000,000	250,000	100	277	365
1,200,000	100,000	158	439	578
600,000	50,000	223	620	813
300,000	25,000	316	877	1,149
120,000	10,000	500	1,389	1,818

DISCUSSION

The Validity of the Data

An elaborate investigation by the Bureau of the Census has determined the completeness of birth registration by comparing the (presumably complete) census data of April 1940 with the births registered in the four preceding months. They found the average proportion of registered births for the entire population to be 92.5%, being 94.0% for whites and 82.0% for nonwhites. The values for whites range from 98.6% in New England to a low of 86.9% in the East South Central States. Registration among nonwhites ranges from a few per cent lower than among whites in the northern states to a low of 73.3% in the West South Central States, in a predominantly Negro population, and only 56.2% in the Mountain States, in a predominantly Indian population. The Bureau of the Census estimates that the overall percentage of births being reported rose by about 3% in both the white and nonwhite groups by 1948. A further discussion of these figures may be found in Vital Statistics of the United States, Part I (1948).

Incomplete birth registration undoubtedly biases certain statistics. For example, the lower proportion of registrations among nonwhites results in too

large a proportion of males being reported, as the white population has almost .9% more males than the 50.6% males among nonwhite births (data compiled from Vital Statistics of the United States, Part II, 1942–1948). Similarly, the proportion of males among registered births is probably increased by the fact that a number of factors operate to give a negative correlation between family size and the probability of a birth being registered (this hypothesis is based on general consideration of present day cultural patterns in the United States). Since a greater proportion of first-born children are males than among later birth orders, the difference being .26% among whites and .13% among nonwhites (data compiled from Vital Statistics of the United States, Part II, 1942–1948), the loss of the data for some large families will be equivalent to the loss of a number of female births. Despite the above biases in the proportion of males registered, there is no reason to suspect the existence of any bias which might affect the registration of births by sex in a seasonal manner. If this assumption is granted, we may suppose that any variation which appears in the data reflects a real variation in the proportion of male births.

One possible exception to this principle may be noted. Records are collected on a yearly basis, and one may look upon the increase in the porportion of registered births as a process of continuous accrual of non-registering families to the registering group. For this reason, December births will always be based on a slightly greater proportion of the population than the January births of the same year, and, as shown in the preceding paragraph, the new registrants will tend to represent groups having lower proportions of males than the families already registering. Over a period of years, this might result in a slightly lower proportion of males in December relative to January than is actually the case, but the effect must be very small.

Evidence For Seasonal Variation

Total U. S. Registration Area. The basic features of a seasonal variation in sex ratio can be seen in the first row of data in table 1. There is a rise from a low proportion of male births in February to a high in June, and then a descent to October. The rise from October to December is of such small magnitude that it cannot be considered as more than a chance variation, and even a movement in the opposite direction could not be precluded. The low sex ratio months of February, March, October, November, and December differ individually from each of May, June, and July at a confidence level of one in ten thousand. Furthermore, if the year is split into spring plus summer births (April through September) as opposed to autumn plus winter births (October through March), there are 51.421% male births in the former period but only 51.312% during the latter. The χ^2 of this difference has a value of 72.5 for one degree of freedom, or a probability of less than .000,000,000,1 that this distribution is due to chance.

Figure 1 shows the remarkable consistency of the features of this curve by comparing the monthly deviations from the average for the three independent periods, 1915–1930, 1931–1936, and 1942–1948. In all three of these there is a sharp drop from January to February, which is the lowest month, followed by a rise to a high period extending through late spring and early summer. The autumn decrease is not as sharply marked as the spring increase, and the variation may be considered random between October and December. January values have been repeated at the right hand side of the graph to emphasize the rise from December, but this rise is significant at the 5% level of probability

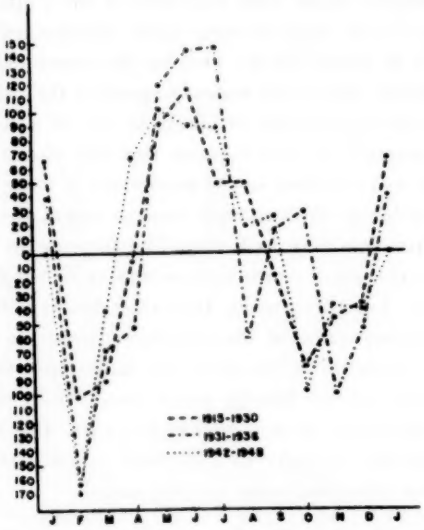

FIG. 1. The proportion of male births per month in the Birth Registration Area of the United States expressed as deviations from the average in units of .001%. The 1915–1930 data have an average of 51.395%, the 1931–1936 data have an average of 51.312%, and the 1942–1948 data have an average of 51.364%.

only in one of the three curves (for the total data the rise from December to January is close to the 1% level of probability). On the other hand, the decrease in proportion of male births between January and February is quite large and is significant at the 1% level of probability for each of the periods.

Basically, the data lead us to the conclusion that the nation as a whole witnesses a slightly larger proportion of male births in the spring and summer than in the autumn and winter. There is a drop between January and February which must be considered real, but the rise from December to January may not be statistically significant in size, and, as previously noted, a small part of this may be due to the increase in proportion of births registered.

Geographical Regions. Among the geographical regions of the United States, there is, in general, agreement on a low proportion of male births in February and March, and again in October, November, and December. Similarly, the high period from May through August appears to be found throughout most of the country.

Because of the small numbers involved, the remarkable shift from the low in January to the high in February for the New England 1942–1948 data is not a significant deviation from the hypothesis that both months are of the same magnitude. If combined with the 1915–1930 data, there is no statistical evidence against the hypothesis that New England is showing the same high in January and low in February that is shown by the whole nation. For the rest of the year, the variation largely agrees with the national trend. The Middle Atlantic States appear to be showing the general pattern and it is probable that the East and West South Central States, the East and West North Central States, and the Mountain States do too. The Pacific States do not clearly belong to this pattern, but if the data for both periods of years are grouped, there is not a clear departure from it. The clearest evidence for a definite departure from the pattern is shown by the South Atlantic States, which present the major features of the seasonal variation, but have the secondary peak in December rather than January for both periods of years. Both the 1942–1948 data taken alone and the two periods pooled are significantly different from expected on the hypothesis that December and January have the same proportion of male births, and the data deviate strongly from expected on the hypothesis that January has the higher proportion of males. This suggests that the secondary peak in January is associated with some phenomenon which proceeds northward in the manner of a seasonal change, but the absence of a similar trend in the South Central regions argues against such an interpretation.

White-Nonwhite Differences. The data comparing the seasonal variation in the sex ratio of the white and nonwhite races for the whole country are of little value since the geographical distribution of the races is not identical. However, almost three-quarters of the nonwhite births are recorded from the south, and these births are divided into two equal groups by dividing the south into the South Atlantic and the (East plus West) South Central States. It is seen that in both racial groups in the South Central States the proportion of males born in January is greater than the proportion born in either February or December. On the other hand, both groups show a higher proportion of males in December than in January in the South Atlantic States, although the values for the white race could possibly be a random fluctuation from a difference which is in the opposite direction. The data for the nonwhites differ at the 1% level of significance from expected on the theory that December and January have the same proportion of male births, and the hypothesis that this is a random deviation from the proportions shown by the rest of the country

would be slightly less probable. However, considering the large number of places in which so radical a departure from the national average could have been found, this single large departure should not be stressed too highly.

Urban-Rural Differences. The urban areas of the United States show the general pattern of a low proportion of males in late winter followed by an early summer high and an autumn low. For the 1915–1930 period, the proportion of males born in January is higher than that for December or February at the 1% level of probability. The January value exceeds that for February in the 1931–1936 data at the 1% level of probability and is higher than the December data at the 5% level. The small cities data, 1931–1936, also show the major seasonal variation. As the total number of births in this category is small, it cannot be stated that the low proportion of males born in January is a departure from the general pattern. The rural areas during both periods of years appear to be showing an autumn and late winter low proportion of male births and a high proportion in summer, although to a smaller extent than in the urban areas. The secondary peak in January may be smaller than that of the urban areas and this peak may include December too.

These data suggested that various selected urban areas should be investigated. New York City, 1915–1930, showed a normal seasonal variation, but the highest proportion of male births in any month occurred in January, which is above both December and February with a probability of error of less than 1%. The percentage differences between January and December or February are several times those for the nation as a whole for the same period and more than twice the differences for the total urban area. The data for New York City are also available by boroughs for the years 1915 through 1923, and for 1929 and 1930. January was above December by 901 units and above February by 806 units in the Bronx, but the small number of births (176,661) kept these differences from being significant. The differences between January and the adjacent months are not as large in Brooklyn and Manhattan, but are larger than those usually found in other regions. Queens showed only a slightly larger ratio in January than either adjacent month, and the small figures for Richmond showed December to be higher than January, though February was distinctly lower. It cannot be shown in these data whether the differences which appear to be present among the boroughs are more probably due to chance or are real. The remainder of urban New York State may be seen, in table 1, to show a secondary peak in January of smaller size than that shown by New York City, and the rural areas of the state show a depression in January. The population is small and the depressed sex ratio during January is not statistically significant, but the failure to follow the pattern of New York City is obvious. Similarly, in New England there is a marked low during January for the rural areas, while the greatest proportion of male births in any month is occurring in the metropolis, Boston, and a moderate January peak is found in

the remainder of the urban areas. Other urban areas (not listed in table 1) have also been investigated. Philadelphia accounts for the major portion of Pennsylvania's peak in January, but Chicago shows a much smaller peak in January than that found for the remainder of Illinois, and Detroit shows a slightly higher peak than the small one possessed by the remainder of Michigan.

The particularly strong January peaks in New York City, Boston, and Philadelphia, the intermediate character of the other urban areas in the region, and the failure of the rural areas surrounding them to show an increased proportion of males at this time, have suggested that the January peak is not due to a climatic difference but to some other factor. The sharpness of the peak, and particularly the fact that December may be high but that February is not, has further suggested that the conditions causing the changed values have a sharp ending. The rural regions in most of the country show enough of a peak in January to offset the low proportion of male births registered in the northeastern rural areas at the same time. Obviously, the odd sex ratio during January is not a simple urban-rural phenomenon.

General Discussion. There does not appear to be any reason to believe that the proportion of male-determining sperm differs from precisely 50%, or that the viability or physiological traits of these sperm are different from those traits in the female-determining sperm. We may suppose that in man fertilizations are accomplished by male-determining and female-determining sperm in equal numbers. This fact would require that if there is a difference in the frequency of the two sexes at birth, some intrauterine cause must be sought. A differential dying off of the sexes during gestation might be tested by investigating the stillbirth records by month. These data were published during the period from 1922 through 1935 in the same volumes in which the live birth records appeared. The average sex ratio of stillbirths is found to be 57.2% males. This percentage is exceeded from April through August, while September and November through January are below average. March is slightly low, but February is high. The monthly deviations are not excessively large, and there are only a few more than a million records. Dividing the stillbirths by month of occurrence into autumn plus winter (October through March) as opposed to spring plus summer (April through September), one finds that a test of the low proportion of males in the former period as opposed to the higher proportion of male births during the latter period results in a χ^2 value of 5.8, which is a departure from equality significant at the 2% level of probability. Therefore, it appears that the spring and summer high proportion of males and autumn and winter low which is found among live births is also found among stillbirths. The records are too few for minor variations in this cycle to be observable. It would seem that death during the later part of gestation does not explain the seasonal variation in the sex ratio which is observed at birth.

The sharp secondary peak in January is a most promising item of information

to investigate. If it is assumed that the sex ratio is related to a phenomenon peculiar to the month of conception, then the phenomenon in question must be restricted largely to April. The possibility that the peak actually occurs earlier in the south suggest that the phenomenon is related to the coming of spring. At best, the data make this a highly tentative guess. Another possibility is that there is a relationship between the occurrence of Lent and the secondary peak in January. It has been found that a number of hypotheses assuming effects due to customs observed during Lent can be advanced, and there is a positive correlation between the distribution of various ethnic groups and the variations in the January sex ratio. To test such hypotheses, the data for the total urban area were divided into those years for which the preceding Easter was early (on or before April 5) and those years for which the preceding Easter was late (on or after April 8). The proportion of males born monthly from December through February is almost identical for the two groups of years, forcing the abandonment of theories related to the occurrence of church holidays based on a lunar calendar.

It may be noted that if the secondary peak in January is due largely to the contribution of only a part of the population, then that segment of the population must have a markedly aberrant sex ratio for January births and the factor which causes this change is a major way in which the sex of a child can be strongly influenced.

SUMMARY

The proportion of live born males in the United States is found to vary seasonally. The highest proportion of male births occurs in the period between May and July, and the lowest proportion occurs from October through March. The features of this curve have a high degree of statistical validity when measured on all births occurring in the United States Birth Registration Area from 1915 through 1936 and 1942 through 1948. The difference between the months having the highest and the lowest proportions of male births for the total U. S. data is only .25%. The data for the individual states have been grouped by regions. It is not certain that all of these regions follow the general trend, but there are no distinct departures from the general pattern of seasonal variation. Similarly, the same seasonal variation may be seen among white and nonwhite and rural and urban groups, and among stillbirths. No hypothesis is found which accounts for the seasonal variation observed.

There is an exception to the general low proportion of males in autumn and winter. For the entire U. S. data, January is the month with the fourth highest proportion of male births. It differs statistically from both December and February. In the northeastern part of the country the rural areas fail to show this exceptional sex ratio, although the urban areas do, and in New York City and Boston a greater proportion of males are born during January than in

any other month. This unusual urban-rural difference does not appear to occur in most of the rest of the nation, and for the entire rural area, January is above average in proportion of male births, despite the low proportion in the northeastern part of the country. In the South Atlantic States, December, rather than January, may be the exception to the low period of the year, and this may be particularly so among the Negro population of these states. No hypothesis appears to account for these facts.

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Qualitative and Quantitative Control of Adult Hemoglobin Synthesis—A Multiple Allele Hypothesis[1]

HARVEY A. ITANO[2]

Gates and Crellin Laboratories of Chemistry[3], California Institute of Technology, Pasadena, California

THE existence of two forms of human hemoglobin, adult and fetal, has long been recognized. Fetal hemoglobin (hemoglobin-*f*) is the preponderant form in the erythrocytes of the fetus and the newborn infant. Beginning in early prenatal life, adult hemoglobin is produced in increasing proportion until, by the end of the first year of postnatal life in the majority of individuals, it completely replaces fetal hemoglobin. In some individuals with chronic anemia, either inherited or acquired, a hemoglobin apparently identical with the normal fetal type (Sansone and Cusmano, 1950; Liquori, 1951; Singer, et al., 1951; Rich, 1952; Itano, 1952; Goodman and Campbell, 1952) may persist.

In addition to the normal fetal and normal adult types, abnormal molecular species of human hemoglobin have been identified in recent years. They appear to be different forms of adult hemoglobin. A hypothesis, that a series of multiple alleles affects the synthesis of the adult hemoglobins, is developed in the ensuing discussion.

The erythrocytes of certain individuals assume crescent-shaped and multipointed configurations when deprived of oxygen. This property, called sickling, is associated in some cases with a chronic hemolytic anemia known as sickle cell anemia or sickle cell disease. In the more prevalent condition known as sickle cell trait or sicklemia, the presence of sickling is not associated with hemolytic anemia. An early study of the inheritance of sickling (Taliaferro and Huck, 1923) led to the conclusion that a dominant allele is responsible for the transmission of this erythrocyte property, but no genetic distinction was made between sickle cell anemia and sickle cell trait. More recently (Beet, 1949; Neel, 1949), it has been postulated that individuals with sickle cell trait are

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[3] Contribution No. 1674.

heterozygous, while those with sickle cell anemia are homozygous, for the sickle cell allele. This holds in the majority of cases of sickle cell disease, but it is now evident that in rare instances a single allele for sickling, when it is combined with a different genetic aberration, produces a disease similar in its manifestations to sickle cell anemia. Four distinct inherited bases for chronic anemia in which sickling cells are present have been described. These will all be included under the term sickle cell disease in this discussion. Only the modification which results from homozygosity for the sickle cell allele will be called sickle cell anemia.

Normal adult hemoglobin (hemoglobin-*a*) is the only form distinguishable in the great majority of non-anemic adults. Both hemoglobin-*a* and sickle cell hemoglobin (hemoglobin-*b*) are present in sickle cell trait erythrocytes (Pauling et al., 1949). Matings of normal individuals with those having sickle cell trait result on the average in equal numbers of children of these two types. Among the progeny of numerous matings of two sickle cell trait individuals, approximately one-fourth of the children have sickle cell anemia, in which the only form of adult hemoglobin is hemoglobin-*b;* one-half have sickle cell trait (hemoglobins *a* and *b*), and one-fourth have only hemoglobin-*a* (Neel, 1951). Hemoglobin-*a* and a second abnormal form of adult hemoglobin, hemoglobin-*c* (Itano and Neel, 1950), are present in non-anemic individuals having the condition called hemoglobin-*c* trait. The children resulting from the mating of a sickle cell trait individual with a hemoglobin-*c* trait individual may be of four types. These are normal, sickle cell trait, hemoglobin-*c* trait, and the modification of sickle cell disease called sickle cell-hemoglobin-*c* disease, in which the two abnormal forms in the parents (*b* and *c*) are both present, and hemoglobin-*a* is absent. A third abnormal hemoglobin, hemoglobin-*d* (Itano, 1951) has been detected in one family. One parent had sickle cell trait and the other hemoglobin-*d* trait, in which hemoglobins-*a* and *d* are present. Two of the children had hemoglobin-*d* trait and two had sickle cell-hemoglobin-*d* disease, characterized by the simultaneous presence of hemoglobins-*b* and *d*.

A fourth form of sickle cell disease evidently results from double heterozygosity in the sickle cell and thalassemia genes and has been observed in matings of individuals with sickle cell trait and thalassemia minor (Silvestroni and Bianco, 1952).

Sickling has been observed only in erythrocytes which contain hemoglobin-*b*. In the various forms of sickle cell disease, a significant correlation has been observed between the degree of anemia and the relative amount of hemoglobin-*b* present (Itano, 1952).

The sickling test is a satisfactory qualitative test for the presence of hemoglobin-*b*, and has been used in studies of the inheritance of the sickling phenomenon. However, electrophoretic analyses and solubility determinations

are necessary to distinguish conclusively the different forms of sickle cell disease as well as to detect abnormal hemoglobins in non-sickling erythrocytes. Electrophoretic analyses also furnish quantitative information on the proportions of the different hemoglobins in a given specimen.

Hemoglobin-*b* separates from hemoglobin-*a* on electrophoretic analysis. Both of these hemoglobins are observed upon analysis of sickle cell trait hemoglobin. In sickle cell anemia hemoglobin, hemoglobin-*b*, together with a small proportion of hemoglobin-*f*, is observed, while hemoglobin-*a* is absent. The qualitative results of electrophoresis are, therefore, in accord with the heterozygous-homozygous theory for the inheritance of sickle cell trait and sickle cell anemia. However, the quantitative studies on the hemoglobins from 42 genetically unrelated individuals (Wells and Itano, 1951) demonstrated the presence of a wide variation in the relative amounts of hemoglobins *a* and *b* in sickle cell trait. The ratio of the hemoglobins remains constant in a given individual with change in time. The effects of age, sex, some environmental factors, and heredity were examined, and the first three factors were found to have no appreciable influence on the ratio of the two hemoglobins in a person with sickle cell trait. In addition to the 42 unrelated subjects, one family of four individuals with sickle cell trait was examined, and the two children were found to have the same ratio of hemoglobins as one of the parents. Subsequently this ratio was investigated in seven families in which sickle cell trait was detected (Neel, et al., 1951). In some of these families the ratio was constant; in others the ratio differed among different individuals in a family. The genetic mechanism for this variability was not clear.

Additional data on the inheritance of hemoglobin ratios became available with the discovery of families in which both hemoglogins *b* and *c* were present (Itano and Neel, 1950; Kaplan, et al., 1951). The electrophoretic data on the members of these families again suggested the existence of a genetic control of hemoglobin ratios.

RESULTS OF FAMILIAL STUDIES

All of the available data on familial studies of hemoglobin ratios are given in Table 1. The ratios were determined by electrophoretic analyses in the Tiselius apparatus. The experimental conditions, reproducibility, and constancy of the ratio in a given individual have been previously discussed (Wells and Itano, 1951). Family Mc is here reported for the first time. The rest of the data have been derived from previous investigations (Wells and Itano, 1951; Itano and Neel, 1950; Neel, et al., 1951). Direct ratios (a/b, a/c, and b/c) rather than percentages are given in order to facilitate analysis of the data. Figure 1 shows the frequencies of these ratios in the families under study. The ratios 1.4 and 1.9, which correspond respectively to 42 and 34 percent sickle cell hemoglobin, occur most frequently. A similar bimodality was observed among 42

TABLE 1. FAMILIAL ELECTROPHORETIC DATA ON HEMOGLOBIN RATIOS

FAMILY	REF.*	Hb PRESENT AND RATIOS		RATIOS IN CHILDREN WITH 2 FORMS ADULT Hb†		
				S.C. Trait	Hb-*c* Trait	S.C.-Hb-*c* Disease
		Father	Mother	*a/b*	*a/c*	*a/c*
Pe	1	*a/b*, 1.9	*a/b*, 1.4	1.5, 1.5		
Sn	2	*a/b*, 1.4	*a* only	1.4, 1.3, 1.4, 1.3		
Wi_1	2	*a* only	*a/b*, 1.4	2.1, 2.2, 1.9, 2.2		
Wa	2	*a/b*, 1.9	*a* only	1.5, 1.4, 1.4, 1.5, 1.9, 1.9, 2.1, 1.9		
Hi	2	*a* only	*a/b*, 1.9	1.9, 1.8		
Li	2	*a* only	*a/b*, 2.6	1.9, 1.8, 3.5		
St	2	*a/b*, 1.7	*a* only	1.3		
Bo	2	*a/b*, 1.2	*a* only	1.3, 1.4, 1.2, 1.3		
Ca	3	*a/c*, 1.8	*a/b*, 2.0		2.0	0.8
Wi_2‡	3	*a/c*, 2.3	*a/b*, 2.2			0.9, 1.0
Mc	—	*a/b*, 2.0	*a/c*, 2.9	2.9		1.0

* (1) Wells and Itano, 1951; (2) Itano and Neel, 1950; (3) Neel, et al., 1951.
† See Table 2 for data on other children.
‡ The mother in family Wi_2 is one of the children in family Wi_1.

Key to Table 1

a, Normal adult hemoglobin
b, Sickle cell hemoglobin
c, Hemoglobin-*c*

Hb, Hemoglobin
S.C., Sickle cell

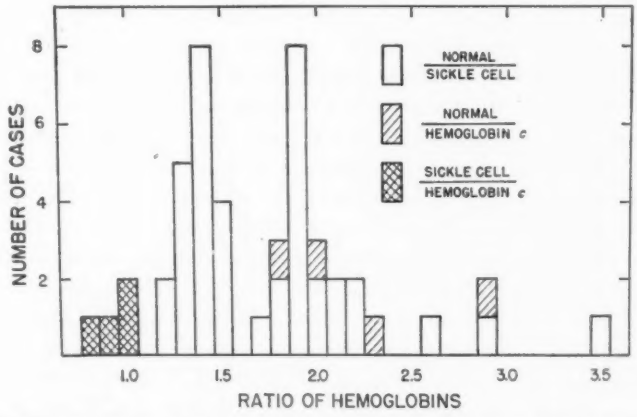

FIG. 1. Frequency distribution of adult hemoglobin ratios in the eleven families included in the present study.

unrelated individuals. Ratios approximating 3 occur in two of the families. With one exception, the ratio of hemoglobin-*b* to hemoglobin-*c* is 0.9 or 1.0. The individual in whom the ratio is 0.8 has a third component, which was

originally reported to be normal adult hemoglobin. Recent studies indicate that this third component is fetal hemoglobin (Itano, 1952).

DISCUSSION

The Allelic Control of Adult Hemoglobin Abnormality

As a point of departure, we can recognize the existence of three genotypes with regard to a single pair of alleles. Letting *sk* represent the normal allele, and *Sk* the sickle cell allele, the three genotypes are *sksk* (normal), *skSk* (sickle cell trait), and *SkSk* (sickle cell anemia). The absence of hemoglobin-*a* in sickle cell anemia suggests that the *Sk* allele controls a complete absence or modification of an essential step in the biochemical differentiation of this form. The question now arises: how are the genetic bases of the other abnormal adult hemoglobins (*c* and *d*) related to the *sk* locus?

According to the results of electrophoretic analyses, the sickle cell allele diverts less than half the total adult hemoglobin production in sickle cell trait to the net synthesis of an abnormal hemoglobin. While making no assumptions for the present as to the genetic control of hemoglobin-*c* synthesis, we may note that in hemoglobin-*c* trait, the observed proportion of hemoglobin-*a* has always been higher than that of hemoglobin-*c* (Table 1). In sickle cell-hemoglobin-*c* disease, the two abnormal hemoglobins, *b* and *c*, are present in nearly equal proportions, and hemoglobin-*a* is absent.

In discussing the relationship of inheritance studies to these biochemical observations, let us first assume that the locus of the gene which is responsible for the abnormal nature of hemoglobin-*c* is different from the *sk* locus and consider the implications of this assumption. The hemoglobin-*c* allele may be designated as *C* and its normal allele as *c*. Accordingly, in families Ca, Wi_2, and Mc, the results of the mating, *Sksk cc* × *sksk Cc* have been observed. Four phenotypes have been recognized among the children, and these would presumably be of the following genotypes: *sksk cc* (normal), *Sksk cc* (sickle cell trait), *sksk Cc* (hemoglobin-*c* trait), and *Sksk Cc* (sickle cell-hemoglobin-*c* disease). According to this genetic analysis, a normal pathway for hemoglobin synthesis may be available in sickle cell-hemoglobin-*c* disease. However, hemoglobin-*a* is absent, although the electrophoretic results cited above suggest that the net effect of *sk* or *c*, acting independently, is greater than that of their respective aberrant alleles, *Sk* or *C*. It is difficult on the basis of these observations to postulate a biochemical mechanism whereby the genotype *skSk cC* would result in the complete absence of hemoglobin-*a*. The most plausible alternative postulate is that *Sk* and *C* are allelic; i.e., no normal allele is present at the *sk* locus in this disease.

We shall therefore postulate that the control of the net synthesis of hemoglobins *a*, *b*, and *c* resides in allelic genes. Each individual receives one member

of this multiple allelic series from each of his parents. Investigations of the sickling properties of sickle cell trait erythrocytes (Sherman, 1940) indicate that in all probability each erythrocyte contains two hemoglobins, *a* and *b*. This allelic series, therefore, acts on a cellular basis, displaying a direct relationship between the genetic constitution of the cell and the type of hemoglobin synthesis it is able to perform. In addition, each individual possesses a separately controlled mechanism for the synthesis of fetal hemoglobin which is latent in most adults but which may be activated in chronic anemias.

The Allelic Control of Rate of Hemoglobin Synthesis

In every specimen of sickle cell trait hemoglobin which has been examined electrophoretically, the percentage of hemoglobin-*a* has been higher than that of hemoglobin-*b*. The mean corpuscular hemoglobin (MCH) of sickle cell trait erythrocytes is normal, so that if the total capacity of the hemoglobin-*b* synthetic mechanism were that represented by its contribution in sickle cell trait, the MCH of sickle cell anemia erythrocytes would be low. Actually the MCH is normal or higher than normal in sickle cell anemia; even if the fetal hemoglobin which is found in sickle cell anemia is taken into account, the amount of hemoglobin-*b* per cell is in the majority of cases more than twice that found in sickle cell trait. A similar phenomenon has been noted in sickle cell-hemoglobin-*c* disease.

The postulate of allelic determination of adult hemoglobin types implies that the relative amounts of two forms of adult hemoglobin in a given individual represent the net result of hemoglobin production by two simultaneous processes. The ratios in sickle cell trait erythrocytes indicate that the net rate of synthesis of hemoglobin-*a* averaged over the entire period of hemoglobination of an erythrocyte, is always higher than that of hemoglobin-*b*. But the relative rates of normal and aberrant hemoglobin synthesis differ among individuals with sickle cell trait. The normal MCH of sickle cell anemia erythrocytes suggests a longer than normal period of synthetic activity by a mechanism which produces an abnormal hemoglobin at a lower than normal rate. The observed variations in the hemoglobin ratios in sickle cell trait may result from the existence of rate modifications in the net synthesis of either or both of the adult hemoglobins present.

Consideration of the data in sickle cell-hemoglobin-*c* disease is of value in deciding whether the hemoglobin-*b* mechanism has more than one rate modification. In contrast to sickle cell trait, this disease is characterized by a hemoglobin ratio which varies but slightly among individuals. In eight individuals from seven different families, the ratio of hemoglobin-*b* to hemoglobin-*c* lies in the narrow range 0.8 to 1.0 (Itano, 1952). The most probable explanation for the relative constancy of this ratio is that only one characteristic rate is associated with the synthesis of each of these hemoglobins, so that whenever

they occur together, their ratio is the same. The assumption of more than one rate modification for one mechanism would necessitate the same assumption for the other; and we should also have to assume that in the individuals examined to date, the corresponding rate modifications of the sickle cell and hemoglobin *c* mechanisms have always occurred together. The multi-modality of the hemoglobin ratios (Figure 1) and the lack of more than two of the modal ratios in any given family of sickle cell trait individuals (Table 1) suggest the presence of a relatively simple genetic control of these ratios.

We shall, therefore, postulate that the variations in the hemoglobin ratios in sickle cell trait are the result of genetically controlled modifications in the rate of synthesis of hemoglobin-*a*, but not of hemoglobin-*b*. This postulate leads to the simplest genetic hypothesis consistent with the data, namely that the inherited synthetic mechanisms for the synthesis of hemoglobin-*b* and hemoglobin-*c* have only one characteristic rate apiece, which are nearly equal, and that the normal mechanism exists in the population as three genetic modifications which produce hemoglobin-*a* at relative rates 1.4, 1.9, and 3 times that of the hemoglobin-*b* mechanism. Of the 47 ratios shown in Figure 1, only 5 deviate more than 15 percent from the assigned ratios, and the maximum deviation is 21 percent. As far as the available data are concerned, we may consider that the hemoglobin-*b* mechanism, the hemoglobin-*c* mechanism, and the three rate modifications of the hemoglobin-*a* mechanism depend on alleles. The individual members of the families considered in this study have been classified according to their postulated genotypes in Table 2. It may be seen that the assumption of multiple allelism does not result in any inconsistencies between the hypothesis and the data.

Genetically this assumption implies that there is a locus at which the occurrence of a mutation may result either in the formation of an abnormal molecular form of hemoglobin or merely in the alteration of the rate of formation of normal adult hemoglobin. According to this hypothesis the ratios in the sickling offspring of the mating of a normal and a sickling individual are determined solely by the genetic constitution of the non-sickling parent. Such an individual receives the *Sk* allele from his affected parent, and one of three alleles governing normal adult hemoglobin synthesis at a particular relative rate from his normal parent. The presence of two, but no more than two, ratios among the sickling children is readily explained on this basis; other explanation as, for example, independent "modifying factors" (Neel, et al., 1951) would lead to different results, less readily compatible with the genetic data as they exist. The data are by no means conclusive, however.

Terminology

The symbol *Sk* has heretofore been employed for the allele responsible for the formation of sickle cell hemoglobin and *sk* for its normal alternative (Neel, et

al., 1951). This terminology will be retained with the necessary modifications to specify each of the five postulated alleles. Sk^b and Sk^c will represent the alleles which result in hemoglobin-*b* and hemoglobin-*c* respectively. The three rate-characterized alleles for hemoglobin-*a* may be designated as $sk^{1.4}$, $sk^{1.9}$, and sk^3. An allele, $sk^{2.2}$, would provide better agreement with the data for families W_1 and Wi_2; other intermediate ratios have been observed among unrelated individuals. More extensive familial studies must be conducted before we can determine whether normal alleles other than the three postulated ones exist in the population.

The assumption of three alleles which result in the formation of hemoglobin-*a* at different rates suggests that an individual who is of the normal phenotype

TABLE 2. POSTULATED GENOTYPES DERIVED FROM FAMILIAL ELECTROPHORETIC DATA

FAMILY	PARENTAL COMBINATION (FATHER × MOTHER)	NUMBER OF CHILDREN									
		S.C. Trait			Hb-*c* Trait			S.C.-Hb-*c* Disease Sk^bSk^c	Normal† $sk\ sk$	S.C. Anemia Sk^bSk^b	Not Tested
		$sk^{1.4}Sk^b$	$sk^{1.9}Sk^b$	sk^3Sk^b	$sk^{1.4}Sk^c$	$sk^{1.9}Sk^c$	sk^3Sk^c				
Pe	$sk^{1.9}Sk^b$ × $sk^{1.4}Sk^b$	2	0	0	0	0	0	0	0	1	0
Sn	$sk^{1.4}Sk^b$ × $sk^{1.4}sk^{(1.4)}$*	4	0	0	0	0	0	0	4	0	1
Wi_1	$sk^{1.9}sk^{(1.9)}$* × $sk^{1.4}Sk^b$	0	4	0	0	0	0	0	1	0	3
Wa	$sk^{1.9}Sk^b$ × $sk^{1.4}sk^{1.9}$*	4	4	0	0	0	0	0	5	0	1
Hi	$sk^{1.9}sk^{(\ )}$* × $sk^{1.9}Sk^b$	0	2	0	0	0	0	0	6	0	1
Li	$sk^{1.9}sk^3$* × sk^3Sk^b	0	2	1	0	0	0	0	4	0	0
St	$sk^{1.9}Sk^b$ × $sk^{1.4}sk^{(\ )}$*	1	0	0	0	0	0	0	4	0	2
Bo	$sk^{1.4}Sk^b$ × $sk^{1.4}sk^{(1.4)}$ *	4	0	0	0	0	0	0	2	0	0
Ca	$sk^{1.9}Sk^c$ × $sk^{1.9}Sk^b$	0	0	0	0	1	0	1	1	0	0
Wi_2	$sk^{1.9}Sk^c$ × $sk^{1.9}Sk^b$	0	0	0	0	0	0	2	1	0	0
Mc	$sk^{1.9}Sk^b$ × sk^3Sk^c	0	0	1	0	0	0	1	0	0	1

* Probable parental genotype deduced from those of children.

† *sksk* includes all of normal genotypes.

may be one of six genotypes which differ in the rate at which his erythrocytes are hemoglobinated. These genotypes may be distinguished by examining the hemoglobin ratios in the offspring resulting from matings with individuals who have the Sk^b or Sk^c allele. This situation is somewhat analogous to the situation presented by three wild-type iso-alleles of *Drosophila melanogaster* at the *ci* locus (Stern and Schaeffer, 1943). Each of these alleles produces in the homozygous condition the same normal wing venation at the usual culturing temperature of 25–26° C., and special tests are required to distinguish these alleles. Iso-alleles have been defined as alleles indistinguishable except by special tests, and the three alleles of normal adult hemoglobin conform to this definition.

The families in Table 1 and 2 were selected on the basis of the presence of the sickle cell allele, and the parents may be assumed to have among them a random selection of the normal iso-alleles. Eliminating the duplication due to the relationship between Wi_1 and Wi_2, and counting only the genes, the presence of which have been established with certainty, we obtain 8, 12, and 3, respectively, for the incidence of $sk^{1.4}$, $sk^{1.9}$, and sk^{3}, among the unrelated parents. Analysis of the data on 42 unrelated individuals reveals that 16 have ratios of 1.4 or 1.5, and 15 have ratios between 1.7 and 2.0, inclusive. The presence of these modal values has previously been noted. If we consider the ratios in all 42 individuals, we find that all but two of these fall within $\pm$ 15 percent of 1.4, 1.9, and 3, and the maximum deviation is 20 percent. The numbers of individuals in these groups are 22, 16, and 4, respectively. The two independent samplings are, therefore, in rough agreement as to the relative frequencies of the postulated iso-alleles.

Relationship of the Other Human Hemoglobins

We have not discussed the relationship to our hypothesis of the fetal hemoglobin which is present in the erythrocytes of sickle cell disease and other chronic anemias. The production of this form of hemoglobin is probably governed by a mechanism genetically different from the adult hemoglobin mechanisms. Its identification and significance in sickle cell disease have been discussed elsewhere (Itano, 1952). Hemoglobin-*d* has been found in only one family, and one of the parents was not available for hemoglobin studies. Furthermore, this hemoglobin does not separate electrophoretically from sickle cell hemoglobin; its identification depends on solubility determinations. Until a method for the determination of the ratio of sickle cell hemoglobin to hemoglobin-*d* is found, quantitative analysis of the inheritance of this hemoglobin is not possible. In the one family studied, the allele for hemoglobin-*d* behaves qualitatively as a member of the multiple allelic series here postulated.

The Inheritance of Thalassemia

It is of interest to speculate upon the relationship of our hypothesis to the findings in thalassemia, an inherited anemia which apparently results from a different type of abnormality in hemoglobin metabolism. No abnormal hemoglobin is known to be associated with thalassemia, but varying amounts of fetal hemoglobin are present, together with normal adult hemoglobin. The MCH is subnormal, and the primary effect of the thalassemia gene appears to be on the synthesis of normal adult hemoglobin (Rich, 1952). The block in the adult mechanism apparently results in the compensatory continuance of the fetal mechanism. In spite of a marked erythroid hyperplasia of the bone marrow and a relatively mild hemolytic process, a severe anemia and peripheral erythroblastosis are present in thalassemia major. These observations imply

that although there is an increased demand by the peripheral blood for erythrocytes, their rates of maturation and release from the hemopoietic tissues are abnormally low. The low MCH values indicate that the retention of the fetal mechanism and the lengthened time of hemoglobination do not completely compensate for the reduced rate of adult hemoglobin synthesis. In thalassemia minor, similar findings are present to a milder degree. Anemia is mild or absent, and a polycythemia may be present as an apparent compensatory response to the low MCH. It has been postulated that the thalassemia major results from homozygosity in the thalassemia gene and that thalassemia minor results from heterozygosity (Valentine and Neel, 1944).

Although the difference between the major and minor forms is usually pronounced, gradations in the severity of each have been noted, and some "mild" and "moderate" cases have been described (Smith, 1948). The multiple allele hypothesis for the rate of synthesis of normal adult hemoglobin provides a possible explanation for the diversified findings in thalassemia. The thalassemia gene apparently is non-allelic with the sickle cell locus (Silvestroni and Bianco, 1952). The familial, as well as individual, differences which have been observed in the manifestations of thalassemia may be due to differences in the effectiveness of the different genotypes for normal adult hemoglobin synthesis described in this paper, in combination with the independent block to normal hemoglobin synthesis which constitutes the net effect of the thalassemia gene.

In sickle cell-thalassemia, which apparently is due to double heterozygosity in the sickle cell and thalassemia genes (Silvestroni and Bianco, 1952), both normal adult and sickle cell hemoglobins are present, but in contrast to sickle cell trait, the percentage of normal hemoglobin is relatively low (Sturgeon, et al., 1952; Itano, 1952). Although the MCH is low, the average amount of sickle cell hemoglobin per erythrocyte is higher than the corresponding values in sickle cell trait and sickle cell-hemoglobin-*c* disease and greater than half that in sickle cell anemia, suggesting that the thalassemia gene does not impair the rate of synthesis of sickle cell hemoglobin. The resulting preponderance of sickle cell hemoglobin probably is the principal biochemical factor in causing the hemolytic anemia.

CONCLUSION

The hypothesis outlined above has been presented with the realization that although it is consistent with all available data, the accumulation of additional information may require its modification. However, we believe that its presentation at this time is of value for several reasons. First, it introduces the concept of relative rates of synthesis as the determining factor in hemoglobin ratios. Second, it postulates that the ratio of the two inherited forms of adult hemoglobin in an individual with sickle cell trait results from variation in the normal

rather than the sickle cell hemoglobin producing mechanism. This suggests that, contrary to an earlier opinion (Neel, et al., 1951) studies of families in which both parents sickle should be as valuable as those in which only one parent sickles in determining the genetic basis of this quantitative variation. Finally, the number of families available to any one laboratory for study is limited, and the provision of a working hypothesis such as we have furnished might stimulate the collection of critical test data in other laboratories.[4]

SUMMARY

A hypothesis has been introduced which attributes the hemoglobin ratios in erythrocytes containing more than one form of adult hemoglobin to differences in the average net rates of synthesis of the hemoglobins. Differences in the hemoglobin ratios among individuals of a given phenotype (e.g., sickle cell trait) may result from the existence of at least three rate modifications of the mechanism for the synthesis of normal hemoglobin. The simplest genetic hypothesis which is in accord with the available familial data on hemoglobin ratios is that the sickle cell hemoglobin mechanism, the hemoglobin *c* mechanism, and the three rate modifications of the normal hemoglobin mechanism depend on alleles.

The possible applicability of this hypothesis in explaining the presence of hemolytic disease in sickle cell-thalassemia heterozygotes and the variability of the clinical and hematologic findings in thalassemia has been discussed.

Electrophoretic data have been presented on a previously unreported family in which both sickle cell hemoglobin and hemoglobin *c* have been found.

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[4] Since this manuscript was submitted for publication, the author has studied a large family in which hemoglobins *a*, *b*, and *c* are present. The preliminary data for this family are consistent with the multiple allele hypothesis for the control of hemoglobin type, but not of ratios. The results, which will be published in a separate paper, suggest that interactions other than those considered in the present paper may influence the relative rates of hemoglobin synthesis.

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Heberden's Nodes

The Family History and Radiographic Appearance of a Large Family

ROBERT M. STECHER, A. H. HERSH, AND HARRY HAUSER

Department of Medicine and of Roentgenology at City Hospital and the Department of Biology at Western Reserve University, Cleveland, Ohio

INTRODUCTION

HEBERDEN'S NODES are enlargements of the terminal joints of the fingers due to osteoarthritis. They are seen quite frequently in men as a deformity of a single finger which arose in response to trauma, often a baseball injury. In women, however, they occur spontaneously starting in one finger and spreading rapidly to others. The incidence varies widely in the population depending upon sex, age (1), the menopause (2) and particularly upon heredity. It was found that this particular form of osteoarthritis involving the joints of the fingers seemed to be independent of osteoarthritis of other parts of the body (3). It was found also to be independent of obesity and of hypertension (4). Two conditions are important in the development of Heberden's nodes. One is the menopause. In women it was found that Heberden's nodes were first noted within three years of the last menstrual period in one half of 99 cases. The age of the menopause varied from 28 to 56 years. The menopause occurred from 15 years before to 20 years after the onset of Heberden's nodes. An intact nerve supply was found to be essential to the development of Heberden's nodes. Cases were presented showing failure of their development in patients with upper motor neuron lesions, as in strokes; lower motor neuron lesion, as in anterior poliomyelitis; and in peripheral nerve injury (5). The study of a large kindred presented here, including 30 individuals in 3 generations, allows tests of the validity of theories of inheritance on the basis of posted data from smaller sibships previously presented.

Idiopathic Heberden's nodes have been described as a condition which is inherited as a sex-influenced characteristic (6) which is dominant in women and recessive in men (i.e., in heterozygous men the penetrance is zero). This conclusion was based upon the study of pedigrees of 74 affected persons. The affected index cases and their siblings included 127 men and 215 women. The difference in the number of men and women in the group was due to the fact that 72 of the 74 index cases were women. Of the women, 108 of 215 were recorded affected, a 1:1 ratio suggesting that the character depends upon a single autosomal dominant gene. In such a case one parent is invariably ex-

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pected to be affected. Actually, mothers were recorded affected in 25 of 74 families. In 11 instances the mother died before the age of 50, so might have been genetically affected without showing the character. Including parents, grandparents, uncles and aunts, antecedent involvement was recognized in 42 families but was lacking in 32.

Of 127 men in this series, only 4 were affected, so Herberden's nodes in men could not be explained as a simple autosomal dominant. As a recessive in men, the phenotypically normal heterozygous fathers were the source of the disease in the families without affected parents. When the families were divided into two groups, one with an affected parent and the other without an affected parent, correction was applied for small family size on a 1:1 basis and for incomplete penetrance because of lack of age, the families with an affected parent showed 70 per cent of the progeny finally expected affected, and the families without affected parents showed 56 per cent of progeny finally expected affected, the latter fairly close to 1:1 ratio of a dominant trait. The high percentage found in the families with phenotypically affected parents was attributed to the presence of unrecognized heterozygotes among the fathers; since genotypic frequency was found to be 30 per cent, this seemed like an adequate explanation. That Heberden's nodes is sex-influenced, dominant in women and recessive in men, was further supported by findings in 4 families with both parents genotypically affected and affected sons. Of 11 daughters in these families, 8 were found affected, close to the 3:1 ratio expected under such circumstances. In these same families, four of eight sons had Heberden's nodes.

Penetrance is not complete until an advanced age. The incidence of idiopathic Heberden's nodes found by examination of 2,200 white women varied from 0.4 per cent in the fourth decade to 30 per cent in the ninth. Gene frequency analysis based on the assumption that this trait is sex-influenced, dominant in women and recessive in men, proved to be 2.7 per cent homozygous dominant, 27.2 per cent heterozygous and 70 per cent normal. Thus the incidence expected at full penetrance is 30 per cent, the sum of homozygous and heterozygous in women and about 3 per cent, the homozygous dominant in men. In 99 cases where an approximate age of onset was determined, it ranged from 30 to 65 years. The mean age of onset was 48.5 years. Heberden's nodes had developed in three-fourths of the patients by the age of 54 years and of seven-eighths of them by 58 years.

FAMILY HISTORY

A pedigree of this kindred is shown in Fig. 1. It includes data on 30 individuals in three generations. There are 9 affected individuals of whom 6 have been studied clinically with photographs and radiographs. Six other members of the family have been examined and called normal. The first generation shows

three affected sisters and a normal brother. These patients are dead. Their diagnosis rests upon the statements of all the members of the second and third generations. They described these forebears as having enlarged, knobby, deformed fingers, much like those of their living affected relatives.

The oldest sister had a son, a daughter and a pair of identical male twins. One twin died at 15, the other at 62 and their brother at 29. All of these were unaffected. The single son left a daughter who died at 22, also unaffected. The others were childless. The daughter, Emma F., II-4, died at 70 with well-developed Heberden's nodes, as seen in Fig. 2. She has 3 children, a son, 49, and daughters, 46 and 43, all normal.

The second daughter of the first generation had 8 children. Two sons, William, II-5, and Edward, II-10, and one daughter, Alice, II-8, were affected. One daughter, Jenny, II-11, who died at 60, was said to be normal; another daughter, Amelia, II-12, at 58, was found to be normal; a third daughter,

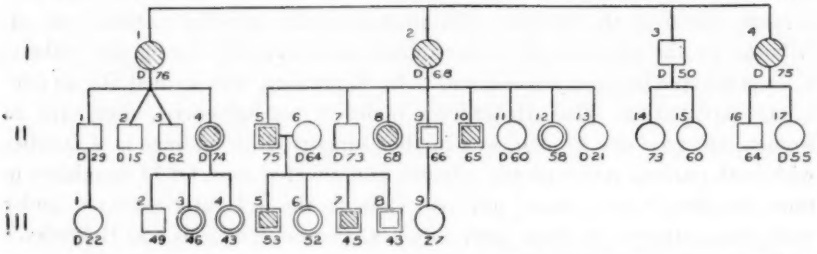

FIG. 1. Pedigree of the S. family showing involvement in three generations. Shaded individuals have idiopathic Heberden's nodes. Symbol with double outline indicates that the individual was examined. Individual II-9 and III-8 have traumatic nodes. II-12 shows islands of bone, which probably represent poor expressivity of idiopathic Heberden's nodes.

Anne, II-13, died at 21; two other sons, John, II-7, who died at 73, and Fred, II-9, living at 66, were normal. The hands of the affected sons and the daughter are shown in Figs. 3, 4, and 5.

William, himself affected, had a normal wife, II-6, who died at 64. This couple had 4 children. The oldest, William, Jr., III-5, has well-developed Heberden's nodes, seen in Fig. 6. His brother, Edward, III-7, has small nodes which are not convincing by appearance, Fig. 7, but changes are seen in the radiographs, Fig. 7A, which justify diagnosing the condition. Their sister, Florence, aged 52, is normal. Their brother, Harvey, III-8, age 46, has an enlarged finger which he definitely states resulted from an injury at work years before. Since no further fingers have become affected, this must be considered as a traumatic Heberden's node.

The third affected sister, I-4, in the first generation had a son and a daughter. They died at 64 and 55 respectively and are described as normal. The son,

I-3, of the first generation has two daughters, 73 and 60, both recorded as negative.

FIG. 2. Photograph of the hands of Emma F., II-4, showing flexion deformity of left fingers 5 and 2 and right 2, 3 and 5. The proximal joints seem normal.

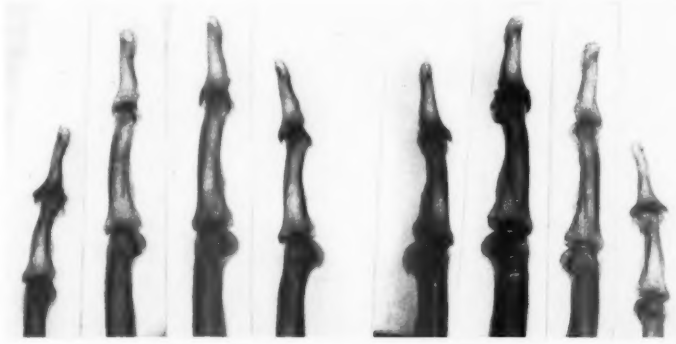

FIG. 2A. Lateral views of the fingers of Emma F., II-4. Definite bony spurs are seen on the dorsal aspect of the distal phalanx, left fingers 5, 3 and 2 and right 2, 3 and 5.

COMMENT

How well do these observations conform to our theory? The three sisters of the first generation are at least heterozygotes, and as such could be expected to transmit this trait to one half of their offspring. Heterozygosity will not be apparent in men and will show only in women who live long enough to develop Heberden's nodes. Two of five women in the second generation, daughters of

affected mothers, are affected. One daughter, age 21, is disregarded. Emma, II-4, of the second generation, is also heterozygous. She may possibly be homozygous, however. The probability that the father is heterozygous is 0.3.

FIG. 3. Photograph of the hands of William, Sr., II-5, showing marked enlargement and flexion deformity of all the distal joints. The left third finger was injured many years before.

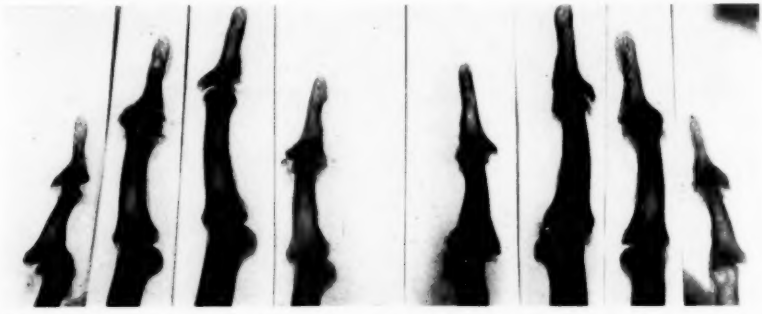

FIG. 3A. Lateral views of the fingers show marked deformity of all the distal joints and changes in the proximal joints of the left 5th finger and the right 2, 3 and 5. The left fingers 4 and 2 show decreased joint space, spur formation and islands of bone. Similar but less marked changes are seen in the right fingers 2, 3, 4 and 5. The left 3rd finger shows a broad buttress of bone with normal joint space and smooth joint surface, indicating that this is probably a traumatic node.

If he had been heterozygous, her chance of being homozygous would be one in 4, heterozygous two in 4. Emma's children have the same chances for homozygosity and heterozygosity. Neither daughter shows Heberden's nodes, but because of their age, they may still develop the trait.

The second family was composed of 8 children, 4 sons and 4 daughters. One of the latter died at 21, so her genotype could not be identified. There were two affected sons and one affected daughter in this family. The mother was affected and, therefore, heterozygous only because some of her daughters

FIG. 4. The hands of Alice G., II-8, showing enlargement and flexion deformity of the left fingers 5, 3 and 2 and the right 2, 3 and 5. Proximal joints do not seem to be deformed. The left 2nd finger showed clinical enlargement with practically no X-Ray change.

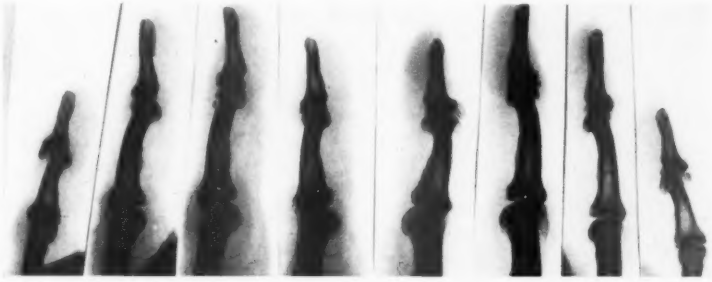

FIG. 4A. Lateral views of the fingers show spur formation on the dorsum of the distal phalanx of the left 5th finger and right 2 and 3, and the distal end of the proximal phalanx of the right 2nd finger. Islands of bone are seen on the left fingers 3 and 5.

escaped. The father must have been heterozygous because sons were affected. Two of the sons are affected and, therefore, are homozygous. In a family of 8, two are expected to be homozygous, four heterozygous and two normal. The four heterozygotes can be accounted for by two phenotypically normal brothers,

one affected sister and the sister who died young. It is possible that the surviving sister, considered normal, is heterozygous with poor expressivity. This sibship is, therefore, completely compatible with the theory.

The next consideration is the family of William, Jr., III-5, and his siblings. It consists of two affected men and their unaffected brother and sister. The father of this family we know to be homozygous because he has Heberden's

FIG. 5. The hands of Edward, II-10, showing slight enlargement of several of his fingers. The right 2nd finger is said to have been injured.

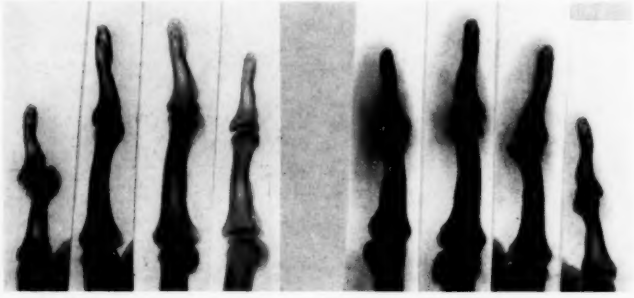

FIG. 5A. Lateral views show marked bone production on the dorsal surface of the distal phalanx of left 5th finger and minor spurs about the distal joint of right 3rd finger.

nodes. His wife must be heterozygous because they have two affected sons. She lived to be 64, but was described as normal. With such a high incidence and consequent experience with Heberden's nodes in the family, it is inconceivable that an advanced degree of the condition could be overlooked. She was not seen, but it is assumed that the mother had lack of penetrance despite her age of 64 or poor expressivity of the disease. Whether she was genotypically

normal or genotypically affected but phenotypically normal because of lack of penetrance or poor expressivity can never be demonstrated.

Florence, III-6, a woman with a homozygous father, must be at least heterozygous and is, therefore, destined to develop Heberden's nodes. She was seen

FIG. 6. Photograph of the hands of William, Jr., III-5, shows marked enlargement of the dista joints of all of his fingers. There is flexion deformity of the left fingers 3 and 2 and the right 2, 3 4 and 5.

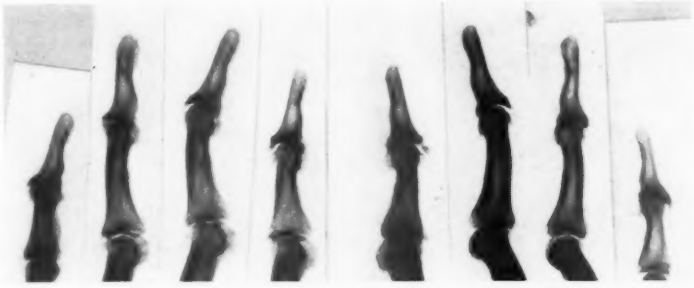

FIG. 6A. Lateral views of the same patient showing changes in nearly all of the distal joints. These consist of spur formation from both the distal phalanx and some from the proximal phalanx and bony islands in both 2nd fingers.

only once at age 52, a little beyond the median age of onset but still much younger than the age of onset in some people. If she survives, she can still develop them. If she were studied radiographically, she might now show evidence of Heberden's nodes with poor expressivity.

RADIOGRAPHIC MANIFESTATIONS

Extensive experience with Heberden's nodes, clinically, photographically and radiologically, during the past 15 years permits recognition of this disease when

FIG. 7. Photograph of the hands of Edward H., III-7, showing only slight enlargement of the left 3rd finger and the right 2 and 3.

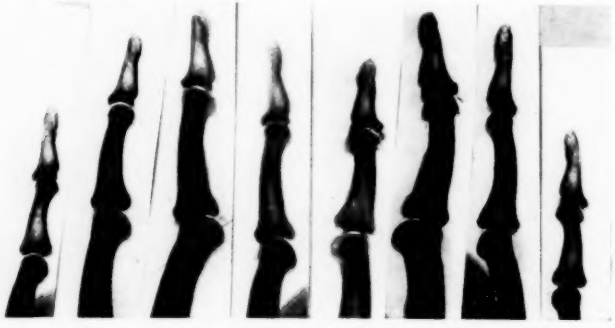

FIG. 7A. Lateral views of these fingers show a slight island of bone on the dorsal aspect of the distal phalanx of the left 3rd finger, a large buttress of bone rising from the dorsal end of the distal phalanx of the right 2nd finger, and bony islands in the dorsum of the joints of the right fingers 3 and 5.

it is of mild degree because of low expressivity. In the original survey, Heberden's nodes were described an enlargement of the joints great enough to be visible and palpable. In severer degrees of the condition, flexion deformity and deviation from the straight line of the finger also occur. Postero-anterior

radiographs of the fingers often show surprisingly little abnormality even when there is considerable enlargement. When lateral radiographs are taken of each finger separately, changes are always seen in clinical cases. At times these changes are very severe. These consist of marked spur formation at the attach-

FIG. 8. Picture of the right hand of Fred, II-9, showing flexion, deviation and enlargement of the right forefinger which occurred as a result of an accident many years before. The condition has remained unchanged.

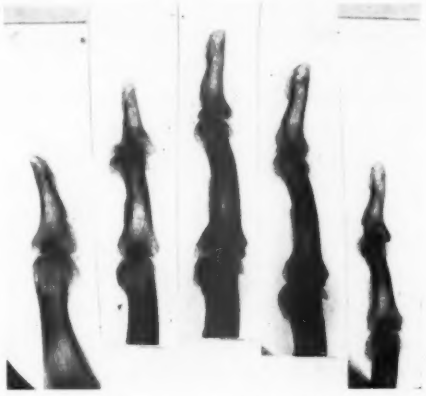

FIG. 8A. Lateral views of all of the fingers of this hand show large bony buttress arising from the proximal end of the distal phalanx of the 2nd finger. The radiograph is turned so that the outline is not exactly seen and the joint space is obscured.

ments of the extensor and less often of the flexor tendons to the terminal phalanx. These are sometimes so large as to form with the normal joint surface a hemispherical mass of bone practically surrounding the distal end of the middle phalanx. At the same time bony spurs are seen arising from the joint margin of the distal cartilaginous surfaces of the middle phalanx.

The technique of taking satisfactory lateral views is difficult and the exact pathological condition is not always revealed. With increased experience a larger proportion of the fingers are properly seen. This means that the long axis of the joint is perpendicular to the film and that the rays are directed through the plane of the joint. As a result, minor changes are noted. These consist of very small bony spurs or bony nodules which are not attached to the terminal phalanx. Lateral views of normal fingers and fingers with rheumatoid arthritis have failed to reveal this minor abnormality except in apparently normal fingers of Heberden's nodes patients or their siblings. It is thought these nodules represent the early manifestation of Heberden's nodes or poor expressivity of the disease.

It is believed that traumatic Heberden's nodes present a different radiographic picture from idiopathic nodes. With traumatic nodes the joint surface is always smooth and round, the joint space is of normal width throughout and the bony growth consists only of a massive, thick enlargement of the dorsal aspect of the proximal end of the terminal phalanx. The radiographic aspects of Heberden's nodes have been described and discussed previously (7).

Enlargements of the fingers are often disappointing in photographs. In this family, the bony enlargement is definitely shown in most of the affected individuals, but it is not well-developed in others.

Photographs of the hands of Emma F., II-4, Fig. 2, show noticeable enlargements of the left fifth and third and the right second, third, and fifth fingers. Lateral radiographs show large bony spurs arising from the dorsum of the proximal edge of the distal phalanges of the right fifth, third and second and the left second, third and fifth fingers. Bony spurs are also seen on the ventral aspect of the left fifth and the right third and fifth fingers. The proximal interphalangeal joints appear normal.

Photographs of the hands of William, Sr., II-5, Fig. 3, show marked enlargement of the terminal joint of all the fingers with flexion deformity of the left second and third and the right third and fourth. Lateral radiograph of the fingers show marked dorsal bony spurs arising from the distal phalanges of all the fingers, from the distal end of the middle phalanges of the right fifth, fourth and second and from all of the fingers of the left hand. Some spurring is seen on the ventral aspect of the left fifth, fourth and second and the right fourth and fifth fingers. Arthritic deformities are also seen in the proximal interphalangeal joints of the left fifth and the right second and fifth fingers.

Attention is called to the left third finger. The distal joint shows a clear joint space and a large solid bony spur extending dorsally from the distal phalanx. This finger was hurt playing baseball at age 18 so severely that the man had to withdraw from the game. This finger had been enlarged for 58 years when the picture was taken and must be considered a traumatic Heberden's node.

Alice's, II-8, hands are seen in Fig. 4. Enlargement and flexion is seen in the right fifth and the left index fingers and enlargement in the right third and fifth fingers. Lateral radiographs show large dorsal spurs on the proximal ends of the distal phalanges of the left fifth and the right index and third fingers

FIG. 9. Photograph of the hands of Amelia, II-12, showing normal looking hands except for amputation of the right ring finger. Clinically no Heberden's nodes are seen.

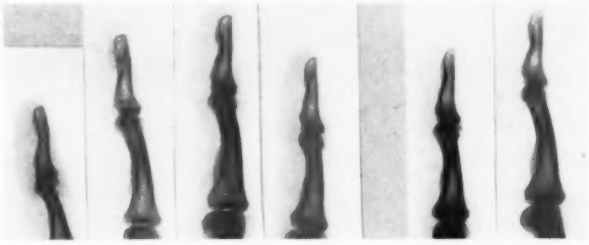

FIG. 9A. Lateral radiographs of the fingers show very small bony spurs or bony islands arising from the dorsal aspect of the distal phalanx of left 5th and right 2nd fingers. Although this patient has been considered to be normal in the pedigree, these bony islands are thought to be early Heberden's nodes or poor expressivity of the condition.

and bone deposits or spurs near the dorsal aspect of the distal ends of the middle phalanges of the left third and the right fifth finger.

Edward's, II-10, hands are seen in Fig. 5. There is enlargement and deviation of the right index finger, enlargement of the right third finger and the left little finger. Lateral radiographs show marked spur formation of the left fifth finger, the right index finger. The third right finger shows a small spur on

the dorsal aspect of the proximal end of the distal phalanx and the distal end of the middle phalanx.

The right index finger was mashed between two bowling balls 40 years before and has been enlarged since then. This is a traumatic Heberden's node.

FIG. 10. Right hand of Harvey, III-6, showing flexion deformity and enlargement of the right little finger, which occurred as a result of an injury some years ago.

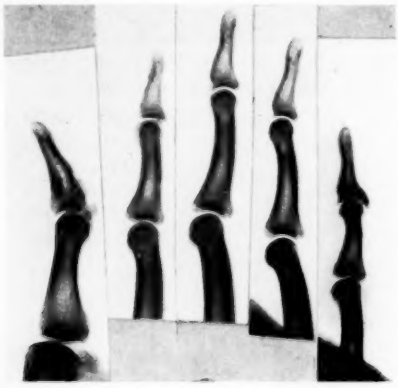

FIG. 10A. Lateral radiographs of Harvey, III-6, showing normal joints, wide joint space, smooth joint surfaces and no spur formation. The little finger shows a large buttress of bone which extends dorsally as a result of injury.

The hands of William, Jr., III-5, the index case, are seen in Fig. 6. Enlargement and flexion deformity are seen in all fingers. Lateral radiographs show marked spur formation from the proximal end of the distal phalanges of the fifth, third and second fingers of both hands.

The hands of Edward H., III-7, are seen in Fig. 7. Enlargement and flexion are seen in the right index, third and fifth fingers. Lateral radiographs show

spur formation at the proximal end of the right second finger and small bony nodules in the same region of the right third and fifth fingers.

Fred, II-9, age 66, is considered normal genetically, but he does show a traumatic Heberden's node on the right index finger, which came from playing baseball forty-six years before (Fig. 8). The other fingers of the right hand are normal. His left hand was lost in an accident at age 10.

The hands of Amelia, II-12, are shown in Fig. 9. They seemed to be completely normal except for the partial amputation of the right ring finger. Lateral radiographs show small spurs arising from the dorsal aspects of the proximal end of the distal phalanx of the left fifth and the right index fingers. This woman is listed as negative because no enlargement of the fingers is seen clinically. These spurs may prove to be true idiopathic Heberden's nodes of poor expressivity.

Harvey's, III-8, hands, Fig. 10, are normal. The right little finger has been enlarged for several years since it was injured at work. Lateral radiographs show a massive spur formation projecting from the proximal end of the dorsal surface of the distal phalanx. This is a traumatic Heberden's node. The man is considered normal genetically.

If these minor aberrations of the radiological picture of the lateral views of the fingers are accepted as evidence of early Heberden's nodes or as poor expressivity of the trait, it allows recognition of genotypically affected individuals who will go unidentified clinically. This concept explains certain inconsistencies in the data which otherwise go unexplained. If this concept proves to be true, it will remove certain exceptions to the rule and nullify arguments against acceptance of the theory that Heberden's nodes are inherited as autosomal sex-influenced characters, dominant in women and recessive in men.

SUMMARY

Previous studies on the nature of Heberden's nodes are summarized, indicating that the idiopathic form of osteoarthritis of the finger joints is independent of other forms of osteoarthritis, of obesity, of hypertension; that it is related to the menopause, it develops only in the presence of normal nerve supply to the hand and fingers, and that it is inherited as an autosomal sex-influenced trait, being dominant in women and recessive in men. The theory of inheritance is tested on a large kindred with 9 affected individuals out of 30 in 3 generations.

Clinical and roentgenological data allow the distinction between idiopathic and traumatic Heberden's nodes. In idiopathic nodes the joint space is narrowed and irregular and spurs arise from the bones about the terminal joint. In traumatic nodes the joint space is usually normal, the joint surfaces are smooth and a heavy bony buttress extends dorsally from the proximal end of the distal

phalanx. Early cases of idiopathic Heberden's nodes can be recognized radiographically when they are not noted clinically by small islands of bone in the extensor tendons near the distal phalanx. This also occurs as a result of poor expressivity, which explains certain heretofore apparent inconsistencies in the data and makes them thoroughly compatible with the proposed theory of inheritance.

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Possible Genetic Factors in the Etiology of Rheumatic Fever[1]

IRENE A. UCHIDA

Department of Zoology, University of Toronto, and Department of Genetics, Hospital for Sick Children

INTRODUCTION

THE tendency for rheumatic fever to run in families has been noted so often that it has become common knowledge. The literature in support of this fact is voluminous. The controversial point lies in the cause of this familial tendency.

It is the belief of some investigators (Faulkner and White, 1924; Griffith et al., 1948) that simultaneous infection is the important cause in the development of rheumatic fever. In a conference of leading workers in the field of rheumatic diseases in England social and economic factors were stressed (Anonymous, 1934).

The strongest advocates of the theory that the susceptibility to rheumatic fever is primarily determined by inheritance are Wilson and Schweitzer. In an intensive study in 1937, these two authors presented evidence supporting the theory that common environmental conditions and communicability are of secondary importance[2].

Analyses of family pedigrees have brought forth evidence in support of three different modes of inheritance. Draper and Seegal's conclusion, that the susceptibility to rheumatic fever is transmitted through sex-linked genes (1923), is based upon a study of 50 families. That a single autosomal recessive gene is responsible is the conclusion reached by Wilson and Schweitzer (1937) after an investigation of 112 families. Single autosomal dominant inheritance is advocated by Beers (1948) on the basis of a single pedigree of four generations. A pedigree of five generations published by Pickles (1943) suggests a similar type of inheritance. So also do pedigrees published by Pribram (1899) and Weitz (1936).

Such in brief is the situation at present in the genetical investigations of rheumatic fever[3]. It seemed important therefore to attempt another investiga-

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[1] From a thesis for the degree of Doctor of Philosophy, University of Toronto. This research was supported by a grant from the National Research Council of Canada.

[2] This study was further extended by Wilson, Schweitzer and Wheeler and republished in a monograph in 1940 by Wilson. In 1943 Wilson, Schweitzer and Lubschez reported a continuation of the original genetic analysis.

[3] Two other papers on the role of heredity in rheumatic fever have been published since this one was submitted: (1) Gray, F. G., Quinn, R. W., and Quinn, J. P. 1952. A Long-term Survey of Rheumatic and Non-rheumatic Families. Am. J. Med. 13: 400–412. (2) Stevenson, A. C., and Cheeseman, E. A. 1952. Heredity and Rheumatic Fever. Ann. Eugen. 17: 177–210.

tion of the genetics of this disease with fresh data in a different country under what would appear to be different environmental conditions. Such a study is now underway in Toronto. Although the size of the present sample is small this paper is being presented at this time because the results of our investigations do not agree with those of Wilson and Schweitzer whose publications represent the most extensive and important work on the subject. Further data are being gathered to extend our study.

METHOD OF COLLECTING DATA

With the co-operation of the Cardiac Clinic of the Hospital for Sick Children and the Department of Public Health, a list of current cases of rheumatic heart disease, rheumatic fever and chorea among children in Toronto and surrounding districts was obtained. The present study, however, includes only those patients who attended the Hospital for Sick Children and who were definitely diagnosed as rheumatic by one physician who is an accepted authority in this field. In this way the diagnosis of all patients was uniform.

For the purpose of obtaining as complete a family history as possible and of recording environmental and economic conditions, visits were made to the homes of those families who showed a willingness to co-operate. To check the accuracy of the family histories all hospital records of any members of the observed families were examined. Contrary to the findings generally reported in the literature this check revealed that with the exception of two unreported cases of rheumatic heart disease all the inaccuracies were found among those who claimed to have had rheumatic fever but who actually had arthritis or rheumatism.

In order to detect any undiagnosed cases among sibs and parents and to check those individuals who claimed to have had rheumatic fever in the past a thorough heart examination of all members of the families involved was undertaken in the Cardiac Clinic of the Hospital for Sick Children by the cardiologist, Dr. John Keith, and his assistant, Dr. Constance Forsyth. In the few cases in which it was impossible to interview and to examine an individual, army reports and hospital records were accepted upon the approval of the examining physicians. There were five parents for whom no records were available and no examination possible because of death or separation. In all these cases the spouse knew of no definite history of rheumatic fever.

Among the parents examined only those who had evidence of rheumatic heart disease or those for whom written records were available or who could report a definite history of illness in bed with the typical symptoms of rheumatic fever were classified as affected individuals. It may be said that this criterion may exclude a number of individuals who were truly rheumatic. Since a check of hospital histories against personal ones revealed that a larger number of

individuals who claimed to be rheumatic were really non-rheumatic than vice versa, the error involved would be smaller on the side of conservatism.

The rigid standards adhered to in this investigation provide strict control of the material used. For this reason as well as for the purely voluntary nature of the study, efforts to gather a larger sample have necessarily been restricted.

DESCRIPTION OF DATA

This study is based upon a group of 58 families with a total of 256 offspring. Children under the age of 2 years have not been included. A breakdown of the material used is given in Table 1.

TABLE 1. SUMMARY OF DATA USED IN THE TORONTO STUDY

	SEX	AFFECTED			UNAFFECTED	TOTAL
		RHD	RF	Total		
Offspring	♂	21	14	35	101	136
	♀	17	15	32	88	120
	Total	38	29	67	189	256
Parents	♂	1	0	1	57	58
	♀	2	5	7	51	58
	Total	3	5	8	108	116

RHD, rheumatic heart disease; RF, rheumatic fever. Those who had evidence of rheumatic carditis at the time of the study were classified as rheumatic heart disease, while those who had never suffered from or who have completely recovered from heart disease are classified under rheumatic fever.

The range for the age of onset of the disease was from 3 to 13 years, with a median age of 7.1 years (males 6.4 years, females 7.4 years). Three females were omitted from this analysis because an accurate age of onset could not be established. For Wilson and Schweitzer's sample the age range is from 1 to 17 years with a median of 4.9 years.

Because of varying environmental influences our sample has been restricted to one economic class, the lower income group. All the families were drawing incomes of approximately $2400 or less per year per family of five. This is the amount necessary to maintain a minimum level of health and self-respect as estimated from the data issued by the Welfare Council of Greater Toronto for 1949.

In order to keep the racial factor as constant as possible the present sample is restricted to "white" families only, of which 7% are of Jewish origin. No definite statistical data are available regarding the incidence of rheumatic fever among the Jewish people except for Hedley's analysis of mortality statistics (1940) in which no difference was noted between Jewish and Gentile populations.

RESULTS

Sex Distribution Among Offspring

Of a total of 120 girls and 136 boys, 26.7% of the girls were affected and 25.7% of the boys (Table 1). There is no significant difference between the sexes. This fact is in keeping with the findings of the 1948–49 Cardiac Registry, a survey of Toronto school children (Gardiner and Keith, 1951).

Sex Distribution Among Parents

In the present sample of 58 families 8 parents were affected. Of these 7 mothers and 1 father were rheumatic. This unusual distribution among the parents may be of etiological importance.

Evidence of Inheritance

a. *Familial Incidence.* Of the 58 families studied there were 8 in which one parent had a positive history of rheumatic fever or rheumatic heart disease. There were no families in which both parents were affected. From Table 2 it is obvious that the type of parental mating, rheumatic or non-rheumatic, made no difference in the incidence of rheumatic fever in the children.

Because ascertainment of affected individuals in the present sample is almost complete Haldane's maximum likelihood method (1932, 1938) is used in this analysis. With the aid of tables supplied by Finney (1949) for the solution of maximum likelihood equations the incidence of rheumatic fever in these families can easily be obtained. For families with one affected parent the incidence is .11 $\pm$ .07 while the incidence in families with both parents unaffected is .08 $\pm$ .03. Since there is no significant difference between these values the data were combined giving a total incidence of .08 $\pm$ .07 (see Table 3).

The frequency of rheumatic fever in the general population of Toronto can be estimated from the results of the 1948–49 Cardiac Registry (Gardiner and Keith, 1951). For the age group 0–15 years the frequency was determined at 2.3 per 1,000. Since it has been shown in surveys of all age groups that the median of the frequency of the age at onset ranges from 12–14 years (Hedley, 1940), it seems safe to assume an incidence of not more than twice the above frequency, i.e. 4.6 per 1,000 or .0046, for the population of Toronto. The frequency in the present sample is obviously much higher than in the total population.

b. *Genetic Analyses.* A strong argument for the importance of genetic factors in the development of a trait is found in the demonstration of a definite mode of inheritance. Accordingly the data were examined in an attempt to determine a definite method for the transmission of the susceptibility to rheumatic fever.

There is no evidence in the Toronto data to suggest a sex-linked mode of inheritance.

In dominant inheritance under ideal conditions of 100% penetrance a trait should be expressed in every generation. Since 86% of the families of the present sample had unaffected parents a low penetrance of 14% is indicated in the parental generation. Among the offspring there is an incidence of .08 (see above) or a penetrance of 16%.

TABLE 2. PERCENTAGE FREQUENCY OF RHEUMATIC CHILDREN OF AFFECTED AND UNAFFECTED PARENTS

TYPE OF MATING	NO. OF MATINGS	TOTAL NO. CHILDREN	% AFFECTED CHILDREN
Both parents unaffected	50	216	26.4
One parent affected	8	40	25.0

TABLE 3. ANALYSIS OF FAMILIES ACCORDING TO NUMBER OF AFFECTED OFFSPRING IN SIBSHIPS OF FIXED SIZE

	NO. OF FAMILIES				
	Both parents unaffected			One parent affected	
No. Affected Offspring / Size of Family	1	2	3	1	2
1	2				
2	4	1		1	1
3	12				
4	11	1		1	
5	5	1		3	
6	6		1		
7	1	1		1	
8	3				
9					
10		1			1
Total	44	5	1	6	2
Incidence	$p = .08 \pm .03$			$p = .11 \pm .07$	
	Combined p value = $.08 \pm .07$				

It has already been pointed out that about equal proportions of offspring were affected regardless of the type of parental mating. This is to be expected under a hypothesis of dominant inheritance with reduced penetrance.

To test for recessive inheritance, the data can be treated in two different ways: (a) by analysis of the offspring and (b) by analysis of the parents.

Among the offspring of matings between two unaffected individuals (both

heterozygous: $H \times H$) there is an incidence of .08 ± .03 (see Table 3), a value which is obviously different from the expected 25% under a hypothesis of recessive inheritance. Similarly an incidence of .11 ± .07 among the offspring of affected by unaffected matings (recessive × heterozygous: $R \times H$) is much lower than the expected 50%.

Analysis of the parents can be made by comparing the proportion of $H \times H$ and $R \times H$ matings. If mating takes place at random (and there is no reason to believe otherwise in the present case) and if the gene frequencies in the population are known, then the expected proportion of matings of $H \times H$ to that of $R \times H$ can be estimated. Because of the nature of the ascertainment of the

TABLE 4. TEST FOR RECESSIVE INHERITANCE OF TORONTO SAMPLE BY RANDOM MATING

SIZE OF FAMILY s	BOTH PARENTS UNAFFECTED ($H \times H$)		ONE PARENT AFFECTED ($R \times H$)		PROP'N OF $H \times H$ MATINGS
	n_s	$N_s = \frac{n_s}{1-q^s}$	n_s	$N_s = \frac{n_s}{1-q^s}$	$p = \frac{N_{H\times H}}{N_{H\times H} + N_{R\times H}}$
1	2	8.0	—	—	1.00
2	5	11.4	2	2.7	0.81
3	12	20.8	—	—	1.00
4	12	17.5	1	1.1	0.94
5	6	7.9	3	3.1	0.72
6	7	8.5	—	—	1.00
7	2	2.3	1	1.0	0.72
8	3	3.3	—	—	1.00
9	—	—	—	—	—
10	1	1.1	1	1.0	0.52
	50	80.8 (90.08%)	8	8.9 (9.92%)	$\bar{p} = 0.85 \pm .06$
Expected prop'ns (incidence .0046)		.0160 (93.02%)		.0012 (6.98%)	

material used, i.e., the presence of the proband in all the observed families, certain adjustments must be made in the analysis of the data*.

An estimate, N, the total number of matings of a particular genotype, can be determined from the observed data by the following:

$$\sum N_s = \sum \frac{n_s}{1-q^s}$$

where n_s is the observed number of families of sibship size s, and $q = \frac{3}{4}$ or $\frac{1}{2}$, the expected proportions of normal offspring from $H \times H$ and $R \times H$ matings respectively. The proportions of matings of $H \times H$ to $R \times H$ can then be compared with the expected proportions based upon the frequency of the trait

* The method used in this analysis was suggested by Professor D. B. W. Reid.

in the general population. The results of this analysis are given in Table 4, the expected proportions being based upon an incidence of the order of .0046 as determined from the Cardiac Registry (see above).

To give some indication of the significance of the difference between observed and expected frequencies estimates of the proportion of $H \times H$ matings for each family size and the simple unweighted average along with its standard error are also given in Table 4. These analyses do not suggest a real discrepancy between observed and expected frequencies.

DISCUSSION

For the inheritance of a predisposition to rheumatic fever two theories have been suggested: single autosomal dominant and single autosomal recessive.

TABLE 5. TEST FOR RECESSIVE INHERITANCE OF NEW YORK SAMPLE BY RANDOM MATING

SIZE OF FAMILY s	BOTH PARENTS UNAFFECTED ($H \times H$)		ONE PARENT AFFECTED ($R \times H$)		PROP'N OF $H \times H$ MATINGS
	n_s	$N_s = \frac{n_s}{1 - q^s}$	n_s	$N_s = \frac{n_s}{1 - q^s}$	$\hat{p} = \frac{N_{H \times H}}{N_{H \times H} + N_{R \times H}}$
1	1	4.0	6	12.0	0.25
2	9	20.6	7	9.3	0.69
3	14	24.2	11	12.6	0.66
4	12	17.5	9	9.6	0.65
5	10	13.1	3	3.1	0.81
6	5	6.1	6	6.1	0.50
7	3	3.5	2	2.0	0.63
8	4	4.4	3	3.0	0.59
9	1	1.1	3	3.0	0.27
	59	94.4 (60.9%)	50	60.7 (39.1%)	$\bar{p} = 0.56 \pm .06$
Expected prop'ns (incidence .03)		.0820 (82.7%)		.0172 (17.3%)	

Beers' theory of dominant inheritance is based upon a single pedigree. Wilson and Schweitzer's theory of recessive inheritance is the result of a series of studies with a group of about 112 families. In Beers' pedigree dominant inheritance cannot be denied because the path of the gene can be traced through four successive generations. The work of Wilson and Schweitzer, however, is open to criticism.

In their analysis of offspring of $H \times H$ matings Wilson and Schweitzer found the observed to exceed the expected frequency by a difference of borderline significance (1940, 1943). In attempting to evaluate this difference the authors conclude that 3 of the parents may have been inaccurately diagnosed as unaffected individuals. A penetrance of 100% is assumed for the offspring of $H \times$

H and $R \times H$ matings while examination of the offspring of two affected parents gives a penetrance of 86%. These two percentages are incompatible and throw doubt upon the theory of recessive inheritance. Furthermore when the New York data are subjected to the above test for random mating, the proportion of $R \times H$ matings far exceeds the expected (see Table 5).

In the present sample the theory of recessive inheritance fits the data as far as the parents are concerned but differs significantly from the observed incidence among the offspring unless a greatly reduced penetrance is taken into consideration. On the other hand dominant inheritance, also with very low penetrance, cannot be ruled out either. For Wilson and Schweitzer's data, however, neither recessive nor dominant inheritance is acceptable.

The conflict between Wilson and Schweitzer's data and the present sample may be caused by differing standards of diagnosis or forceful environmental influences making a comparison of the two groups impossible. The difficulty encountered in the attempt to establish a simple method of inheritance may be the result of these environmental influences or perhaps a more complex method of inheritance is the answer. It is hoped that with a larger sample more definite conclusions can be reached.

CONCLUSIONS

An attempt has been made to evaluate the genetic factors in the development of rheumatic fever. If there is a genetic basis for rheumatic fever, it appears from the existing data that no simple genetic theory can adequately explain the transmission of the susceptibility to the condition. With the publication of Wilson and Schweitzer's studies it was thought that the genetic problems had been solved. However, it is now felt that only a beginning has been made and the work must be continued with much more extensive data.

SUMMARY

The present study is based upon a group of 58 families with a total of 256 offspring. The median age of onset is 7.1 years with a range of 3 to 13 years. The sample is limited to the lower income group and to the white race.

There is no difference in the sex distribution of rheumatic children in Toronto. However, there is a significant difference among the parents, the mothers being more often affected than the fathers.

There is a higher concentration of rheumatics in the present sample than among the general population of Toronto.

Analysis of the present sample indicates that if a greatly reduced penetrance is considered both simple recessive and simple dominant inheritance fit the data but neither of these theories is compatible with the New York data. It is concluded therefore that no definite mode of inheritance can yet be established.

ACKNOWLEDGMENT

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A Pedigree of Syndactylism of the Middle and Ring Fingers

M. F. ASHLEY MONTAGU

Department of Anthropology, Rutgers University, New Brunswick, New Jersey

THE propositus, an attractive white American unmarried female of 22 years of age, showed complete syndactylism of the middle and ring fingers of the right hand. There was a rather sharp curvature of the terminal phalanges, and the nails grew from separate beds. What is remarkable is that while the flexure creases of the skin at the dorsal proximal interphalangeal joints are in proper relation to one another on both fingers, on the palmar surface there is a single

FIG. 1. The right dorsal view of the hand showing syndactylism of the middle and ring fingers. Compared with the normal left hand.

series of flexure creases for both conjoined fingers (see Figs. 1 & 2). The distal interphalangeal joint showed no dorsal or palmar flexure creases, and the terminal phalanges were permanently flexed and not capable of being moved.

Breadth of right hand 87.0 mm	Length of right hand 154.0 mm
Breadth of left hand 84.0 mm	Length of left hand 154.0 mm

The propositus' great-grandfather was of German origin, and it was known that he exhibited the same condition. It was also known that syndactylism had a long history on his side of the family. Of this grandfather's children, six daughters and one son, three of the daughters and the son exhibited the condition, but it is not now remembered which hand was affected. One of these

daughters married and had an only child, a son, who exhibited the condition, it is believed on the right hand. Another of the daughters married and had four sons and one daughter. The youngest son in this series was the only one to be affected, and he exhibited the condition in the right hand. He was the father

FIG. 2. The palmar view of the hands

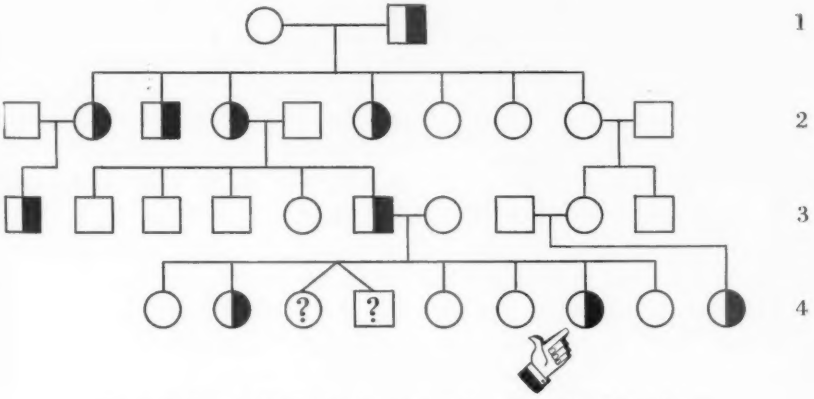

FIG. 3. Pedigree of family showing syndactylism of middle and ring fingers

of the propositus. All five members of this series, in the third generation, died between ages 40 and 50.

One of the daughters in the second generation, who showed no evidences of syndactylism, married and had a daughter and son who were also free of the condition; but the daughter, in this third generation married, and had an only child, a daughter, who exhibits the syndactylism in her right hand.

A sister, four years older than the propositus, exhibits the same condition in the left hand.

The pedigree (Fig. 3) reproduced here indicates that the condition of middle and ring finger syndactylism in this family is probably due to a dominant gene with varying penetrance and expressivity, carried on an X-chromosome.

This pedigree provides further evidence of the fact that some types of syndactylism can be transmitted through both females and males.

SUMMARY

A four generation pedigree of syndactylism of the middle and ring fingers is reported in an American white female. This pedigree provides evidence some types of syndactylism can be transmitted through both the female and male lines. The evidence in this pedigree indicates that a dominant gene with varying penetrance and expressivity, carried on an X-chromosome, is involved.

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The Calculation of Reproductive Fitness and the Mutation Rate of the Gene for Chondrodystrophy[1]

ROBERT E. POPHAM

Department of Anthropology, University of Toronto, Canada

IN HIS comprehensive study of chondrodystrophy and its inheritance, Mørch (1941) provided estimates of the mutation rate of the gene for this anomaly. These estimates, 4.2×10^{-5} by the direct method and 4.8×10^{-5} by the indirect, have generally been accepted as among the more reliable of those which have been calculated for human genes. Stern (1949) employed Mørch's data in his Principles of Human Genetics (pp. 407–410) to exemplify the two approaches to the estimation of a mutation rate. Neel (1952), in a recent general discussion of the study of human mutation, included Mørch's rates for chondrodystrophy in his list of available estimates. However, it is the writer's contention that the indirect estimate of the mutation rate, 4.8×10^{-5}, reported by Mørch, corresponds to an error in the calculation of the relative reproductive fitness of chondrodystrophics.

The determination of relative reproductive fitness depends upon the consideration that a defect such as chondrodystrophy (which is transmitted as an autosomal dominant) generally interferes to some extent with the likelihood of an individual's reproduction. That is to say, the number of children produced by heterozygous carriers of a dominant abnormal allele tends to be less than that of the normal population (Stern 1949). Therefore, relative reproductive fitness may be expressed as the ratio of the average number of offspring produced by affected persons to the average (or an estimated average) for the normal population. Mørch's sample comprised 108 chondrodystrophics, living and dead. Altogether these had 27 children of which one half, theoretically, were chondrodystrophic. Mørch found the fecundity of this group with regard to the abnormal allele to be $\frac{1}{2} \times 27/108 = 0.1250$. The 108 dwarfs had 457 normal sibs who had a total of 582 children. The fecundity of these sibs was held to be, $582/457 = 1.2735$ and, therefore, the relative reproductive fitness (f) of the chondrodystrophics followed as, $0.1250/1.2735 = 0.098$. The error which exists in this method of calculation may be clarified by an example. Suppose that chondrodystrophy did *not* affect reproductive fitness. This would

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mean, by definition, that the chondrodystrophics produced as many offspring as their normal sibs ($f = 1$). In this instance the sibs averaged 1.2735. The 108 dwarfs would therefore have to have 108×1.2735 or approximately 138 children. If this had occurred, the gene frequencies of (D), the allele for chondrodystrophy, in the parental and first generation of offspring would be as follows:

$$\textit{Frequency of } D\textit{, parental generation:} \quad \frac{108/(108 + 108 + 216 + 914 + 914) = .048}{108(Dd) \times 108(dd) \qquad 457(dd) \times 457(dd)}$$

$$\downarrow \qquad\qquad \downarrow$$

$$\textit{Frequency of } D\textit{, first gen. offspring:} \quad \frac{138(69Dd,\ 69dd) \qquad 582(dd)}{69/(69 + 69 + 138 + 1164) \qquad\qquad = .048}$$

It will be observed that the frequency of the dwarf allele has remained unchanged from the parental generation to the offspring as would be expected if the gene did not affect reproductive fitness. But if the relative fitness is now calculated for these hypothetical data by Mørch's procedure it will be found that,

$$f = \frac{(\frac{1}{2})(138)}{108} \Big/ \frac{582}{457} = \text{approx. } \tfrac{1}{2}.$$

It would therefore be necessary to conclude that the chondrodystrophics had a relative reproductive fitness of only $\frac{1}{2}$ and consequently, that the frequency of the gene D had decreased by 50% in the first generation of offspring. As shown above this would not be the case.

Mørch's error lies in the fact that numbers of alleles and numbers of offspring were confused in the calculation of relative reproductive fitness. The abnormal alleles of the offspring of the chondrodystrophics (numbering $\frac{1}{2} \times 27$) were derived from 108 abnormal alleles present in the parental generation. This gives an effective fecundity for the chondrodystrophics of $\frac{1}{2} \times 27/108 = 0.1250$, as obtained by Mørch. On the other hand, the offspring of the 457 non-chondrodystrophic sibs derived 582 of their normal alleles from $2 \times 457 = 914$ parental alleles. The frequency of normal alleles had therefore *decreased* by $582/914 = 0.6368$ instead of increasing by a factor of 1.2735 as maintained by Mørch. Thus, the correct value of f, the relative reproductive fitness of the chondrodystrophics, is $0.1250/0.6368 = 0.1963$. Parenthetically, it may be noted that the same result is obtained if the calculation is performed in terms of numbers of offspring, that is

$$\frac{27}{108} \Big/ \frac{582}{457} = 0.2500/1.2735 = 0.1963.$$

The direct estimate of the mutation rate of the gene for chondrodystrophy, obtained by Mørch, was based upon the occurrence of 10 chondrodystrophics

among 94,075 births in the Rigshospital, Copenhagen over a period of thirty years. Of the 10, two had one chondrodystrophic parent. Thus among 94,073 offspring of normal parents, 8 were chondrodystrophic. This corresponds to one mutant allele in 23,518 or a mutation rate of 4.25×10^{-5}. Substitution of the new value of f, derived above, in the formula

$$u = \tfrac{1}{2}(1 - f)x$$

gives an indirect estimate of the mutation rate of

$$\tfrac{1}{2}(1 - 0.1963)10/94{,}075 = 4.27 \times 10^{-5}.$$

This estimate is in much closer agreement with that obtained by the direct method than is the old value of 4.8×10^{-5} which corresponds to the error in the calculation of reproductive fitness discussed above.

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Research Designs in Psychological Genetics with Special Reference to the Multiple Variance Method

RAYMOND B. CATTELL

Laboratory of Personality Assessment and Group Behavior, University of Illinois, Urbana, Illinois

1. DIRECT MENDELIAN ANALYSES VERY RESTRICTED IN PSYCHOLOGICAL GENETICS

PSYCHOLOGICAL GENETICS is a sadly neglected crossroads embarrassing the main highways of psychology and genetics. In genetics this neglect involves nothing worse than a failure to meet the challenge of unusual methodological difficulties; but in psychology its causes are less reputable and its consequences more devastating. For a psychology lacking any dependable or precise knowledge of innate organizations and influences is bankrupt in its theoretical structure and a charlatan in its clinical and educational practices.

Stimulated by the advances now being made in personality measurement, which promise to make a revival of genetic investigations in this area profitable, it seemed timely to take stock of the problems accounting for the neglect of psychological genetics and to survey systematically the possible methodological answers to them.

In the last resort the difficulties peculiar to human psychological genetics arise from the intangibility and incommensurableness of normal psychological traits. This condition precludes the use of Mendelian units and any method, such as that of population genetics, dependent on ability to recognize unit characters (but not unit dimensions). As in physical traits, the abnormal unit characters so far genetically observed greatly exceed the normal ones, but in mental traits this still produces a mere handful, covering such things as color blindness, some degenerative nervous disorders, such as Huntington's chorea, some forms of imbecility and possibly "violent temper," and some psychotic tendencies. For the great majority of mental characteristics whether normal or abnormal, about which we seek information, are to be observed and measured only in terms of graded continua, and, as such, are almost certainly determined, in the innate contribution, by multi-gene mechanisms.

Because of its seniority, as a science, the psychological geneticist is frequently tempted to lean upon physical genetics as an alternative to the above approach, to the extent of seeking to prove that a mental trait is related to a physical trait and of leaving the physical trait to carry the implication of inheritance.

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When the inheritance of the physical trait, e.g. eye color, is well founded, (best as a unit Mendelian character, less satisfactory if in variance terms,) this research approach is well justified and is not yet sufficiently exploited.

If, however, we consider only that psychological genetics research which stands on its own methods—and that is the theme of the present article—we must recognize that the central difficulty of incommensurableness mentioned above rules out all approaches such as population genetics, the study of genealogies, etc., which depend on infallible recognition of Mendelian units. Close examination shows this rejection of the Mendelian unit approach to stem from three distinct interdictions. First, it arises from inability to demarcate the boundaries of psychological traits. Secondly, it stems from the multi-gene structure which demands more precise instruments than we have for recording increments in such traits even when their form is demarcated. Thirdly, it is augmented apparently by the psychological manifestations of genes proving to have in general lower penetrance or "manifestation rate" (11) than do physical traits, i.e. by their being only rarely completely unmodified by environment. Recent advances in personality (7) measurement have done much to overcome the first of these difficulties and to reduce the second, so that it behooves us to take fresh stock of the methodological position.

Whenever a trait is substantially modified, or at least disguised, by environment, there are broadly two ways known to geneticists by which the interaction of heredity and environment can be quantitatively analyzed and expressed. They are (1) an expression by means of "manifestation rate," penetrance and other related indices, or (2) an expression of the relative variance, in the total variance, due respectively to hereditary and environmental sources of variation. The former devices proceed in terms of Mendelian unit characters, assume that the unit characters and the mechanism can be inferred from certain sources of information, and then calculate the disparity between genotypes and phenotypes in incidence, etc. We shall not consider this further because, as stated above, extremely few psychological unit characters can yet be indubitably recognized as such.

2. EXISTING USE OF VARIANCE RATIO METHODS

The main approach open to the psychologist therefore becomes that of measuring some important and functionally unitary (but not necessarily genetically unitary) trait and determining the nature-nurture variance ratio. In time, with knowledge of such ratios before him, and such increase of precision of measurement as will permit him to recognize step-wise increments, he may hope to explore the gene components in multi-gene dimensions, but that is scarcely for this generation to consider. Meanwhile, immense advances in all aspects of psychology could be achieved by gaining knowledge of nature-nur-

ture variance ratios in a variety of personality, learning, and clinical traits. For among the hundreds of important personality traits and performances psychometrically measured we so far know something about the nature-nurture ratio only in regard to one: general intelligence!

Both the research designs and the formulation of conclusions in the past uses of the method of variance have in the writer's opinion lacked the power which could come from a comprehensive realization of possible developments in the method. There have been far too many studies concentrating on some particular ratio, either as an experimental research means or as a goal of scientific statement, without regard to the *general* variances which should be the ultimate and definitive goal of investigation in the area. For example, more than half of all psychological investigations, e.g. (1, 19, 21, 23, 31, 37, 53) have operated on a comparison of differences of fraternal and identical twins only, in the manner set out by such geneticists as Hogben (24), Gates (18) and others. What a design of this kind effectively tells us is whether the trait has any genetic determination *at all*, (for no one is very interested in the specific intra-familial relations of non-identical twins as such). In short, it does not give a value directly applicable to the variances in which we are most interested in the general population and in common predictions concerning random individuals.

The chief difficulties raised by Loevinger, (32) and others in regard to past uses of the variance method, and some of which require discussion here as relevant to the development proposed below, are as follows:

1. the assumption that influences combine additively.
2. that estimates of the experimental error involved in measurement have not been allowed to enter into the computations.
3. the assumption that environment acts in a random manner in relation to heredity and thus lowers the intercorrelations of relatives.
4. the assumption that the ratios found have a universal reference.
5. the assumption that environment produces its greatest influence on variance when it is most varied.

As to the first, it will be noted that this is the assumption behind practically all current biological statistics, e.g. the method of variance, the multiple correlation coefficient, factor analysis etc. Admittedly it is likely that some real relationships are in terms of higher order equations. For example, the increment in reasoning power produced by an increment in education is probably greater at a higher than at a lower I.Q. But in the initial scientific structuring of a field we have to proceed by the first approximation to higher order relations presented by the additive equation, and where several variables are involved, this is likely to be close enough to permit us to see the next step to be taken.

No one doubts that there is "dynamic interaction" of heredity and environment, but though such phrases sound more vital than the statistician's simple

combination of the two influences they are apt to be also more mystical, vague and remote from experimental confirmation: Dynamic interaction can presumably be expressed in terms of hypothesized quantitative consequences. Eventually it would seem desirable to work out, in the light of findings with the simple additive assumption, the expectations from a variety of more complex assumptions, to see which hypothesis better fits the facts. To reduce the guesswork in such hypotheses formation, it would seem desirable to investigate the additive variance ratios over *various small ranges within the total scatter*, subsequent to researches of the present nature on the whole range.

On the desirability—indeed, necessity—of not confusing experimental error variance with one of the variances to be compared, there can be no serious question; though a recent study (15) apparently disagrees with Loevinger's particular strictures on the matter. The design proposed here takes account of the reliability and validity of the measures in the subsequent computation.

One of the reasons for the development of this design is the avoidance of the third source of doubt indicated above. It is assumed that hereditary and environmental influences may be significantly correlated. However, Fisher's argument remains true that, short of perfect correlation of heredity and environment the effects of environment will *tend* to attenuate the correlation of relatives due to heredity. An example of a possible positive correlation is that more intelligent children will generally have had a better informed environment created by their more intelligent parents. An example of a negative correlation is that dominant parents may create more submissive reactions in their children. An example of spurious invocation of the principle is the argument that the very same environment is more "stimulating of intelligence" for a more intelligent child. By environment we must mean environment, not some unmeasurable and illogical intermediate variable called "the meaning of the environment."

Even the argument for significant correlations in the first two examples *may* be doubted. A well-informed environment may increase information, but not necessarily intelligence. Since aspects of the environment are altogether different in kind from aspects of the biological organism, it may be doubted whether the varied potential manifestations of a genetic factor can have a significant *mean* correlation with the collection of diversified variables in the environment which stimulate each, for the mean of any random set of correlations is likely to be zero. Incidentally it is certain that no meaning can be ascribed to a generally "favorable" or "unfavorable" environment when one is dealing with at least a dozen independent dimensions of personality, each measured from a pole chosen with indifference as far as value judgments are concerned. Accordingly, each dimension in this investigation is treated separately, and while the possibility of correlations is investigated we do not expect more than a few to exceed chance.

As to criticism number four no student of statistics would assume that the

discovered nature-nurture variance ratio applies beyond the culture pattern and the racial, genetic sample involved. Where the genetic sample is less varied the environmental variance will have a greater influence, and where the culture pattern gives either equal or no opportunity to all, the importance of hereditary variance will increase. Thus ratios do not converge on a "general answer" but are particular to societies and specific to traits. The time for further study of the meaning of the variance ratios will come when the distribution has been found in a whole series of cultures and genetic samples, as well as for a whole series of personality traits.

The fifth and last of the above complications cannot be dismissed with a brief contingent or permanent solution as can the others. It involves far-reaching concepts requiring more prolonged consideration. The essential notion here, supported by some experimental evidence, is that a more restricted environment does not always produce a more restricted variance in the manifest trait, and vice versa. Hogben (24, 32) even asserts that traits may increase in variance as environmental variance decreases, and one can certainly imagine situations, e.g. in the dynamic field a greater array of morbid expressions with narrower conventions of sex or dominance; in the biological field a greater variance in activity with a milder temperature range, where this *could* occur.

While there is not space here to deal exhaustively with the matter, our contention will be that this matter can be handled by regard for approximate statistical and mathematical formulations. Many of these cases could be handled, like some problems in factor analyses, by rescaling the environmental units, and in extreme instances this would involve putting a curvilinear relation into a linear form by ordering the environmental measures in terms of their influence upon the organism, before beginning investigation of variance relationships. In others, principally in the dynamic field, this might amount to the variance being scored from both extremes toward the middle. Certainly we must expect the effect of environmental variance to be a function of the mean level about which variation occurs. However, provided facts making such further analysis possible are recorded in the data, it is appropriate to proceed on simpler assumptions until the appearance of inconsistencies with other experimental findings indicates the need in certain cases for more specific inquiries along these lines.

3. IMPORTANT AND OBTAINABLE VARIANCES

The new development described here begins with a comprehensive framing of the problem in which is asked (1) What are the variance ratios we most want to know, both for applied predictions and for understanding personality development theory? and (2) What is the full tally of naturally existing social and biological groupings upon which we could possibly operate experimentally to arrive at these ratios?

As to the first, it is evident that one variance ratio with which we must always be concerned is that of heredity and environment in their operation upon the *general population* of any given society. Next we recognize that the variance existing between *families*, either environmentally or genetically, is a statistical quantity of considerable importance, for most people are raised with two parents and certainly all are born of them. In most circumstances, and where we make a personality prediction, we are concerned with the fraction of variance in the population due to family heredity (i.e., inter-familial hereditary variance) and family environmental background (i.e., inter-familial environmental variance). Also we are concerned with the corresponding intra-familial variances. For any calculation of where the individual will stand in the final outcome, in the observable personality distribution, depends on various relationships of these. Closer examination of these variances and their relative practical importances however, must be postponed for more precise discussion until after we have dealt with point two above, i.e. the fractions of variance which are experimentally available in naturally occurring groups.

What we ideally seek in these group breakdowns are sub-groups of the *same* heredity in which there are *differences* of environment and groups of the same environment in which there are differences of heredity. Although we may not find any situations quite so simple as to provide *total* reduction of one source of variance, the teasing out of the influences of heredity and environment is still possible where there is *some* degree of homogeneity in one i.e. where the two can be made to some extent to vary differently. In short, analysis requires the comparison of the observed variances in two or more situations in which we know of at least *relative restrictions* in the ranges of heredity or environmental influences. It is then possible that by suitable combinations of these measured variances we can obtain the important ratios required. Objections raised by some critics of heredity-environment studies to the attempt to hold "heredity or environment constant" should note that here we seek not to hold a single variable "constant," but to significantly vary the *relative* variances. First, let us take a look at the available instances of hereditary variance restriction, which would seem to be as follows:

A. *Hereditary Groupings*	*Degree of Genetic Homogeneity*
1. Uniovular twins	Identity of genes
2. Siblings and fraternal twins	Identity of parental genes from which segregation has occurred
3. Other family relationship groupings, e.g. parents, cousins	Various common gene fractions
4. Socio-economic classes, ecological communities, e.g. villages, and other partially restricted intrabreeding groups	Genetic homogeneity hard to estimate
5. Groups chosen to be homogeneous for inheritable physical traits, e.g. blood groups, races, etc.	Homogeneous for one or more gene patterns, according to genetic nature of physical traits

The two last are too vague in boundary, too specialized in area of homogeneity and sometimes too irrelevant to most prediction problems with which individual psychology is concerned to justify their being systematically examined in further formulations developed in this article. Nevertheless they deserve thorough consideration in social psychological problems, to which they are often highly pertinent.

Restrictions of environmental variances occur in the following:

B. *Environmental Groupings*	*Degree of Environmental Homogeneity*
1. Persons belonging to the same family: a. Husband and wife b. Parents and children c. Siblings and foster siblings d. Twins[1]	Identity of family atmosphere, i.e. experiencing the same *intra*-familial variance only
2. Children raised in same orphanage, boarding school or similar "large family"	Homogeneity likely to be less than in family and not so comparable from sub-group to sub-group
3. Persons belonging to the same sub-group institutions, e.g. church, social class, school, army, club, political party	Homogeneity localized in total personality habit system, in that institutional impact is restricted to some habits and is not continuously applied
4. Persons belonging to same nation or culture pattern (6)	Influences total personality
5. Persons subjected to identical controlled, experimental training experience in some limited area of personality, or selected for similarity of incidents in personal histories	Limited area of homogeneity

(Heredity or environmental differences associated with sex difference are to be included as a special category in 3 above.)

It must be recognized at once that there is, and can be, no isomorphism—no simple reciprocity—between the character and degree of the genetic and the environmental restrictions provided by the groupings in A and B. Thus, while it is possible to have genetically identical individuals, it is not possible to have, at least among human beings, with their susceptibility to remote and symbolic communication, environmentally identical individuals. Likewise the environmental uniformity of, say, a church's doctrine and laws, is in no way the counterpart of the limitation of genetic homogeneity in the third or fourth hereditary groupings above.

The only restriction which is roughly analogous in the two domains, which is perhaps of approximately equal efficacy and certainly of equally prominent social importance, is that represented by the fields of inter-and-intra-familial similarity of heredity and inter- and intra-familial similarity of environment. The coincidence of these family groupings in relevance for prediction and con-

[1] In any refined treatment of the problem we must recognize that the similarity of environment for twins differs significantly from that of siblings generally, as many writers (36, 53) have argued; though in different directions!

venience for experiment will be found to make them key elements in the designs discussed below.

4. THE ROLE OF EXPERIMENTAL CONTROL OF VARIANCE

Before proceeding to discuss how the above-listed, naturally-occurring groupings of restricted variance can be used to reveal desired ratios, it seems desirable to make a digression to satisfy a possible question in the reader's mind as to how far the experimentally-produced restrictions—B(5) above—may be developed in potency to the point where the proposed work with naturally-occurring restrictions might prove unnecessary.

In texts on scientific method generally it has frequently been pointed out (7) that there is a continuum of design from complete experimental control (as in a "crucial experiment") where no statistics are necessary, to complete inability to use experimental control, where the whole analysis of relations has to be statistical treatment of events *in situ*. Most physical science investigation enjoys the former and most social and biological science is compelled to the latter. Whenever we can deliberately control, to any desired degree, a situational or an organismic variance, we have one variable fewer to be deduced by statistical computation and inference and if we have under our control all but the dependent variable we are happy indeed. To gain control and reduce degrees of freedom is thus always desirable if it can be done without losing the ability to concern ourselves with some behavior manifestation which occurs only in the freer and larger situation. For example, the laws of learning can be studied better in the laboratory, with controlled experiences, than by trying to equate experiences in everyday life, by statistical means; but if true neurosis occurs in life far more typically and powerfully than in the laboratory, the effect of neurotic conditions on learning is better investigated by statistical analysis of nature's untidy experiments than by more extensive control of variables in the laboratory situation.

Extensive control of genetic and environmental variances is possible in animal experimentation and there is no reason why psychological genetics should not advance rapidly in terms of animal behavior, as illustrated by the excellent work of Stockard (49), Rundquist (41), Tryon (52), Scott (44), and others (see 45). But for a long time there will be difficulty, owing to the relatively great differences between men and other mammals, especially in cerebral structure, in translating these results confidently to man. And where we are concerned to get nature-nurture ratios regarding the relative effects of particular social institutions and culture patterns the animal experiment approach is obviously impotent.

Turning from such attempts to investigate human psychology by animal proxy, to direct research on man, one is faced with the impossibility of heredity experiments and the severe restriction of experimental control of environment.

The experimental designs possible and so far used mainly employ the plan of subjecting co-twins, or hereditarily equated (by sampling) control and experimental groups to differential training in some specific behavior area small enough to be tolerated as a matter of human behavior control. Unfortunately, if such experiments[2] continue long enough for definite results, genetically produced maturation changes become an indeterminable part of the change observed, and though this part is equal in the case of identical co-twins its indeterminateness prevents any assessment of the true relative importance of nature and nurture from such an experiment alone. However, the approach designated under B(5) above would yield valuable evidence if energetically exploited, especially in conjunction with other results. Meanwhile, since our interest is in major aspects of personality, and long-term, standard social influences, we shall return to the methods of statistical analysis *in situ*.

5. THE PROPER ROLE OF THE "MULTIPLE VARIANCE DESIGN"

The writer's intention is now to take the available specific sub-group variances in heredity and environment set out in section 3 above and demonstrate that by suitably combining them in an over-all design a more complete solution of the relevant variance ratios is possible than this approach has before achieved.

Pioneer work in psychological genetics, using the comparison of one or two of the above variances has been initiated by Holzinger (25), Burks (2), Cattell and Molteno (5), Leahy (29), (see 34, 35) and others. Indeed our only firm knowledge of the degree of inheritance of general intelligence rests on such studies.

The more radical methodological advance which is being proposed here is, as stated above, to go beyond handling variances in pairs and *to solve for all of them simultaneously by bringing data on all into a related set of equations.* This proposal has somewhat the same relation to the designs so far used as does factor analysis, with its simultaneous extraction of all possible relations among several variables, to the classical experiments which determine relations of variables only in pairs. In general the comparison of only two variances gives us a ratio of very limited utility and leaves some of the most important variance undeterminable. What shall here be called the *multiple variance design*, as described below, aims to produce enough simultaneous equations to solve for all the variances involved and also for the correlations among the variances.

However, in this first presentation we shall concentrate on those variances which are of greatest theoretical importance and practical utility. As pointed

[2] A design sometimes discussed and applied (43) which assumes that traits which become more diversified with age are more environmentally determined than those which do not, is invalid for this same reason.

out above these center upon the special effects of the family as a biological and social institution. In fact the variances we most need to know, in any one personality source trait for most theoretical and practical purposes, are:

1. The total variance in that trait for the given society.
2. The fraction of that variance due to societal hereditary variation.
3. The fraction of that variance due to societal environmental variation.
4. The fraction of that variance due to people being born of different parental pairs.
5. The fraction of that variance due to people being brought up by different parental pairs i.e. in different homes.
6. The fraction due to different genetic segregations among children of the same parents.
7. The fraction due to environmental differences of the kind that can exist among children brought up by the same parents.

For clarity of subscripts we shall speak of "between" and "within" instead of "inter" and "intra" familial variance, representing the former adjectives by *B* and *W*. We shall also represent family and society by the subscripts *f* and *s*, and hereditary and environmentally conditioned variances by *h* and *e*. The total variance, not split into *h* and *e* components, will be written *O* (observed variance) for it is this and this only that we can actually measure. The above seven variances would thus be written: σ^2_{sO}, σ^2_{sh}, σ^2_{se}, σ^2_{Bfh}, σ^2_{Bfe}, σ^2_{Wfh}, and σ^2_{Wfe}.

One of the false simplifications which has had to be adopted in past work has been the assumption that hereditary and environmental influences are uncorrelated. Thus the total observed social variance has been assumed to be the sum of hereditary and environmentally determined variances, whereas strictly:

$$\sigma^2_{sO} = \sigma^2_{sH} + \sigma^2_{sE} + 2r\sigma_{sH}\cdot\sigma_{sE} \tag{1}$$

where *r* is the correlation existing between the environmental and the hereditary sources of variation. In the case of intelligence there is considerable circumstantial evidence that innate ability and social status are positively correlated, for the collation of results for general and culture free tests indicates a correlation of around +0.3. *If we were to accept the doubtful sociological conclusion that higher social status is identical with the dimension of increased environmental stimulation of intelligence*, then we should have to insert 0.3 for *r* in the above equation. This value is taken only for illustration since it is not proposed to accept here as a precisely dependable entry even the evidence of a culture free test (3) on the *r* of intelligence and social stimulation of intelligence, still less the assumption that higher status gives more stimulus to intelligence. Indeed the only adequate procedure is to *solve* for *r* from the simultaneous equations provided by the experiment, instead of depending on extraneous inferences

If we agree that the family is the most important and practical subgroup for the breakdown of variance we can proceed systematically to survey the possible measurements and equations for this purpose. Incidentally, extending the consideration to comprehend other groups is pointless unless we are specifically interested in them, for although they bring new data (and corresponding new equations) they also bring new unknowns. Let us first list in Table 1, the sources of variance which we suppose to be entering into observable variances. As the correlations among these variances (i.e. the correlation of an individual's deviation in one with his deviation in the other) will enter, as in equation 1 above, we also set out systematically the correlations that will be required.

Since in the formulae which follow it will be cumbersome to write in full the letter subscripts to the various correlation coefficients, number subscripts will later replace the letters in the way indicated.

TABLE 1. SOURCES OF VARIANCE TO BE CONSIDERED AND THEIR POSSIBLE RELATIONSHIPS

SOURCES OF VARIANCE	1	2	3	4	5	6
1. Hered. det. var. between families (σ^2_{Bfh})						
2. Envir. det. var. between families (σ^2_{Bfe})	r_{12}					
3. Hered. det. var. within families (σ^2_{Wfh})	r_{13}	r_{23}				
4. Envir. det. var. within families (σ^2_{Wfe})	r_{14}	r_{24}	r_{34}			
5. Total hered. det. var. in society (σ^2_{sh})	r_{15}	r_{25}	r_{35}	r_{45}		
6. Total envir. det. var. in society (σ^2_{se})	r_{16}	r_{26}	r_{36}	r_{46}	r_{56}	

Now let us set out in equations the way in which various observable, measurable variances would be made up of these hypothetical sources of variance. In each case we shall indicate in words, to the left of the equation, what experimental measurement, i.e. what data would be required, and the breakdown into our sub-sources of variance on the right. We shall number systematically only those equations arising from practically feasible measurements. The first of these equations should concern the total population variance, which is made up of every one of these sources, as follows:

$$(2)\quad \text{Total societal population variance} = \sigma^2_{sO} = \sigma^2_{Wfh} + \sigma^2_{Wfe} + \sigma^2_{Bfh} + \sigma^2_{Bfe} + 2(r_{34}\sigma_{Wfh}\sigma_{Wfe} + r_{13}\sigma_{Wfh}\sigma_{Bfh} + r_{23}\sigma_{Wfh}\sigma_{Bfe} + r_{14}\sigma_{Wfe}\sigma_{Bfh} + r_{24}\sigma_{Wfe}\sigma_{Bfe} + r_{12}\sigma_{Bfh}\sigma_{Bfe})$$

This equation simply breaks down the total, observed variance in any source trait, which is easily determinable, into the variances within and between families. It has ten unknowns, but, as we shall see later, we may not have to have ten equations, since there is every reason to believe that some of the r values do not differ significantly from zero. However, we will continue to find out what equations are empirically *available*.

(3) Within family (Intersibling) variance $= \sigma^2_{WfO} = \sigma^2_{Wfh} + \sigma^2_{Wfe} + 2r_{34}\sigma_{WfH}\sigma_{Wfe}$

(4) Variance of siblings reared in different families $= \sigma^2_{Bfe} + \sigma^2_{Wfe} + \sigma^2_{Wfh} + 2(r_{24}\sigma_{Bfe}\sigma_{Wfe} + r_{23}\sigma_{Bfe}\sigma_{Wfh} + r_{34}\sigma_{Wfe}\sigma_{Wfh})$

(5) Variance of non-siblings reared together $= \sigma^2_{Bfh} + \sigma^2_{Wfh} + \sigma^2_{Wfe} + 2(r_{13}\sigma_{Bfh}\sigma_{Wfh} + r_{14}\sigma_{Bfh}\sigma_{Wfe} + r_{34}\sigma_{Wfh}\sigma_{Wfe})$

(6) Variance of identical twins reared together $= \sigma^2_{Wfe}$

The above equations should be reviewed in the light of the *mathematically possible* number of combinations of the four variances, to see that no feasible combination has been missed. Among four there would be four single terms, six double, four treble and one quartette. If situations could be found in which variances could be subtracted as well as added many more combinations would be possible with sign patterns, but none occur. Of the four singles the two purely hereditary variances are unusable, since identical environments cannot be created. The two purely environmental variances are identical twins within one family (σ^2_{Wef}) and the "between family environmental variance," which is impracticable alone for reasons given below. Of the six expressions with two variance terms on each one corresponds to identical twins reared apart (not proposed above because impossibly rare), one to siblings reared together ((3) above), and four to practically impossible measures. They are impossible because, like the single term case just rejected above, they contain a "between family" variance term without the corresponding "within family" variance term; and, so long as one deals with differences, can never be obtained without including the effects of "within family" differences. The same appearance of a term without its naturally occurring partner invalidates two of the four mathematically possible combinations of three terms. The quartette is, of course, entirely practicable, as the total societal variance. Thus we have the five usable equations indicated above, though one might also be tempted to consider using one or two of the non-individual (group) differences, one of which is readily practicable, namely the sum of this between-family-environment variance and between-family-heredity variance, obtainable by taking the variance (or the differences of random pairs) of the "mid-siblings" for normal families, i.e. sibs reared in their own families.

Statisticians may be interested in the relation of this multiple component variance analysis to the standard procedure of analysis of variance. The latter would have the advantage of dealing with more variance components, of being able to solve for all interactions, and of yielding immediate significance tests; but the distribution with which cases occur in nature causes differences in the numbers in the cells (most cells, moreover, having zero or one case), making this whole procedure extraordinarily complicated.

However, we must consider also some experimentally difficult but feasible combinations which might be substituted for some of the above equations in such a way as to eliminate the unknown r values by reducing them to zero. Thus although there may normally be a correlation between family heredity and environment, if we could find whole families of true siblings brought up in foster families to which (as families) they are randomly allocated, we could then assume this r_{23} to have no real significance.

The equation, which we have most regretfully omitted from our series of practically applicable equations, because it is not empirically obtainable, has been mentioned above and is set out below. The most zealous individual investigators have only turned up about twenty cases of twins reared apart, from birth; so we must conclude that nothing but an ideally endowed research project could hope to utilize this equation.

$$\text{Variance of identical twins reared apart} = \sigma^2_{Wfe} + \sigma^2_{Bfe} + 2r_{24}\sigma_{Wfe}\sigma_{Bfe}$$

If the reader wishes to return to consideration of the possible introduction of the other naturally occurring subgroups of hereditary and environmental homogeneity listed at the end of section 3 he will see that no addition of these would bring in more equations than unknowns.

There is sometimes an apparent gain from the uncorrelatedness of these different sources. For example, one could obtain data on (a) unrelated persons, (b) siblings and (c) identical twins raised in the same orphanage, and if the variances are uncorrelated this would add only one unknown and three new equations. But these other natural subgroups bring specific disadvantages, notably the difficulty that orphanages are not sufficiently of one species to give confidence in or utility to "within orphanage environmentally determined variance" unless all the hundreds of cases required could be obtained in one orphanage. The likelihood that the variances would be uncorrelated can probably be considered higher in these situations, but if freedom from correlation cannot be assumed this would bring in three new equations and four new unknowns. In general, the inclusion of new degrees of restricted hereditary relatedness, e.g. cousinship, parent and child, or of new patterns of restricted environmental variance relationship, e.g. same school, urban dwelling only, etc., would be profitable, then, only in the following conditions:

1. that the equations bring in the new relation at least twice.
2. that the equation does not have more than two terms, so that unknown r values do not accumulate.
3. that the restricted grouping be of a repeatable "species" or "type" within society.
4. that the variance in the restricted group be significantly different both from that in the total group and from zero, so that difference terms will be clear and unequivocal values.

Since each new equation also requires further experimental data before the whole analysis can begin, too many equations are undesirable also on experimental grounds. Indeed in the interests of a design suited to the limited means of most experimenters, we must now proceed to adopt a particular compromise of widest utility. Our suggested compromise is to use the five numbered equations above, permitting us to solve for the *four* unknown variances and *one* of the correlation coefficients. We shall justify this compromise on the grounds that to the best of our indirect knowledge only one of the correlations concerned has any significant value, the rest being equal to zero. Alternatively we could insert the indirectly estimated value for this r and then solve for any one of the other r values about the zero value of which some reasonable doubt may exist.

Another modification which may have to be considered is that of recognizing that family environmental variance for twins may be different from that indicated for siblings. We have, then, six equations and six unknowns for which we can obtain a general solution still yielding the required proportional contributions of the portioned variance. The fact that the family environment is probably different for twins than for siblings is obvious even if only because of the age factor. Beyond this, the very fact of being a twin, and the resultant attitudes toward this similarity, can be considered an important variable in personality study tending to differentiate between twins and ordinary siblings.

Of the six r values which enter into the above equations the only one almost *certain* to have significance is r_{12}—that of inter-familial environment and inter-familial heredity; for, if only because of the correlations of both with social status we may expect some tendency for families of more "effective" hereditary endowment to have more favorable environmental conditions. Accordingly we shall assume this has to be solved for and shall set the other r values at zero. The alternative would be to estimate this correlation, at least for such source traits as intelligence and emotional stability, to be about 0.3, (9) (10) (3) (4) (21) (31) (48); to insert this in the equation and look for one more questionably zero r for which to solve. Of the remaining five correlations (r_{13}, r_{14}, r_{23}, r_{24}, r_{34}) perhaps some argument could be found for expecting significance in r_{34} since the hereditarily unusual child in the family may excite environmental unusual reactions from the other family members. Incidentally it would be quite wrong to suppose that in general and for all personality factors "favorable" heredity goes with "favorable" environment. Indeed the whole notion of "favorable" or "good" becomes meaningless for personality factors e.g. surgency-vs-desurgency, to which no ethical or social valuations can be intelligibly attached.

6. THE DESIGN WORKED OUT FOR A SPECIFIC PROBLEM

The multiple variance method will now be fitted to a particular research, both for illustration and to foreshadow the specific research on heredity in

personality which the writer is carrying out for the National Institutes of Health, Public Health Service. This investigation sets out to explore for the first time the nature-nurture ratios on twelve personality factors for which reasonably reliable objective measures have at length become available.

The test batteries are to be administered to eleven and twelve year old children, since it is most likely that by taking children instead of adults we can obtain consistent residence in one family up to the age concerned, and also gather cases more readily. Naturally it is desired to take as few cases as are likely to give reliable ratios.

Now the variances described above can either be measured (for each personality factor separately) directly by measuring the populations concerned and calculating the standard deviations, or indirectly from the correlation coefficient. Thus if we have one hundred families, in each of which one sibling is paired with another, whereupon $r = 1 - (\sigma_d^2/2\sigma^2)$ (20). Similarily, if we take random individuals in the general population their variance (in standard score) will be unity, which is what we would also get if we took $1 - r^2$, for r in the general population should be zero.

To obtain the five equations shown to be required by the discussion of the previous section we need tests on a sample population of (a) identical twins in their own families, (b) siblings in their own families, (c) siblings each member of pair in a different family, (d) unrelated persons in pairs in the same families, (e) unrelated persons in different families. Since the individuals used for (c) can also be used, in another combination, for (d), and similarly (e) overlaps these groups, the total to be tested is not five times the number required for any one category. There is little point at this stage in making any estimate of the standard error of the desired nature-nurture ratio in terms of the number of cases (and the individual variance standard errors) since we are tied by the endowment of the experiment to a necessary minimum. This minimum we have made 100 pairs in each category, thus requiring a testing of 350 to 450 cases in all. (The latter number is preferable and indicates the use of a separate group for (e)).

As usual, the two kinds of error to be considered are those of sampling and of measurement, the first of which is sufficiently defined by our total above—providing we take pains to make our cases a random sample from the range of environmental and hereditary variation in the general population. The error of measurement will be defined by the reliability coefficients for our various personality factor tests. There is danger of this error variance becoming confounded with the environmental variance (when hereditary variance is nil) and hereditary variance (when environmental variance is kept small). For our statements about the first fraction, i.e., that derived from the r, apply only to the reliable variance in our tests. This matter can only receive proper evalua-

tion when we find in our populations the actual reliability coefficients of our tests. Correction for attenuation may then be employed.

In summary, it is planned to test 100 each of five different populations, in pairs, and by using five simultaneous equations to solve for the 4 variance unknowns and one unknown r, thereby obtaining nature-nurture ratios in the form of a general solution.

Comments by geneticists on this research design before it proceeds to final analysis will be appreciated. Further, the author would be grateful to anyone bringing to his notice cases in the Mid-West region of 10–14 yr. old siblings reared apart from birth—for this category of case is the most difficult to obtain.

The writer wishes to acknowledge the valuable criticisms made by his colleagues Dr. W. Gruen, Dr. W. E. Kappauf, Dr. C. Blythe, Dr. L. L. McQuitty, and especially the value of discussion with Dr. D. R. Saunders (42), Dr. L. Penrose and Dr. J. B. S. Haldane. The investigation is supported by a research grant from the National Institutes of Health, Public Health Service.

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Further Notes on the Pedigree of Idiopathic Convulsive Disorder

MADGE T. MACKLIN

Department of Medicine, Ohio State University, Columbus, Ohio

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AFTER the paper appearing in the December issue of this journal was accepted, Mrs. Louise Overton, a graduate student in genetics, pointed out to me that the pedigree would be just as well explained if the mutant gene were in the Y chromosome of the husband of II 1, not shown in the figure, and whom I will refer to in this note as II 1 *a*. This would involve only 5 crossovers and 11 non-crossovers; but there is an equal probability that the mutant gene might have been on the X chromosome of II 1 *a*, entailing 7 crossovers and 9 non-crossovers, making an average crossover value of 37.5 if II 1 *a* is regarded as the starting point of the mutant gene.

The pedigree, as it stands, is also equally explainable on the supposition that the mutant gene arose in the second generation, but in II 1 herself, rather than in I 1 or even in a parent of I 1, thus providing both I 1 and I 2 with the gene. This hypothesis that the mutant gene arose in II 1 involves 8 crossovers and 6 non-crossovers, giving a *cov* of 57.1 per cent.

The statement of Palmer and Snyder that VI 2, although as far as was known was not related to his wife VI 1, yet carried the same surname of III 1 and by implication of II 1 *a*, may indicate that II 1 *a* was in fact the person whose gene was duplicated in all seven of the affected offspring in generation VII. This would bring the marriage between VI 1 and VI 2 into line as a consanguineous mating, explaining the appearance of the recessive defect in the offspring. With the surname being the same, VI 2 is probably connected with II 1 *a* by an unbroken line of males, thus reducing the number of crossovers relative to the number of times the gene was transmitted by a male. This latter is an assumption which may not be valid, however, for Palmer and Snyder further state that the surname of IV 4 in the figure, therefore also of IV 2, (two sisters who married into the family) had the same surname as their husbands, so that many more related marriages are probably occurring in this pedigree than appear on the surface, and the persons connecting II 1 *a* and VI *2* may not all be males, hence involving more crossovers.

The points made in my original paper are still valid, however, namely, (1) that ***with the pedigree as presented in the article of Snyder and Palmer with the interpretation being that it was through either I 1 or through both I 1 and I 2 that the mutant gene was descending***, a range of crossover values can be estimated,

and (2) that the average is so near to 50 per cent, as to make it indistinguishable in this small sample from the independent assortment expected in the case of an autosomal gene. *Only if the mutant gene is coming from II 1 a*, rather than from II 1 as a starting point, or through her forebears, is partial sex-linkage the preferable explanation.

Attention should be called to the fact that the line connecting the two males in the first generation of the pedigree should be a sibship line, not a marriage line as in the figure (1).

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BOOK REVIEWS

Eugenics, Galton and After

By C. P. BLACKER (General Secretary, Eugenics Society, Physician Bethlem Royal Hospital, Honorary Secretary, Population Investigation Committee etc.) London: Gerald Duckworth and Co., 1952. Pp. 349, with 11 tables, 4 plates and 4 diagrams. 25s.

DR. BLACKER devotes about a third of his book to a brief but fascinating account of Galton's life and major contributions to science. Galton was a precocious child (with an intelligence quotient which Professor Terman estimates at no less than 200), but he did not distinguish himself at the university where, perhaps because of a near breakdown, he failed to take hoped-for honors in mathematics. Active throughout a long life, he did his best work, in the author's opinion, after he had passed the age of sixty.

Coming into an adequate fortune at the age of twenty-two, he abandoned the medical studies on which he had embarked and, on behalf of the Royal Geographical Society, began a reconnaissance of previously unmapped areas in southwestern Africa. His geographical explorations bringing him into contact with native tribes aroused an interest in anthropology, and this in turn led to his preoccupation with racial and individual differences. He introduced important anthropometric and psychometric techniques and, among other things, seems to have been the first to perceive that "identical twins were a heaven sent gift to the student of heredity". His recognition of the phenomenon of "co-relation" and his development of the correlation calculus are contributions which rank with the genetic contributions of Mendel, who was born the same year as Galton. It was Galton who initiated the eugenics movement and who founded the now famous Eugenics Laboratory at the University of London. Two quotations will serve to indicate his approach to the subject. "Man is gifted" said Galton "with pity and other kindly feelings; he has also the power of preventing many kinds of suffering. I conceive it to fall well within his province to replace Natural Selection by other processes that are more merciful and no less effective. This is precisely the aim of eugenics." And again, "It is above all things needful for the successful progress of eugenics that its advocates should move discreetly and claim no more efficacy on its behalf than the future will confirm; otherwise a reaction will be invited."

There have been times, as most of us recall, when Galton's admonition was little heeded; and the reaction he feared did set in. We are presented with a penetrating discussion of factors underlying this reaction, including reverberations of such idealogical concepts as nazism and "soviet genetics", which in turn have conspired to create the impression that all ideas of improving the racial germplasm are either suspect or futile. The great problem of the moment is a demographic one; "preoccupations about quality do not naturally arise until the purely numerical question takes on a certain aspect". The Malthusian dilemma has not been resolved; it still confronts the world. The author recognizes and discusses in considerable detail five phases in the demographic cycle: (1) *high stationary*, birth and death rates both high; (2) *early expanding*, high birth rate, lower or falling death rate; (3) *late expanding*, both birth and death rates declining, the latter more rapidly; (4) *low stationary*, birth and death rates both low (but likely to be unstable); (5) *declining phase*, with an excess of deaths over births. The future would seem to depend on a successful and more or less simultaneous solution of the problems created by the different phases of this cycle. "The world can scarcely be safeguarded from war until a solution is reached." In a discussion of

proposed methods of control, from subsidies on the one hand to birth control on the other, the author brings to bear the fruits of his many years of careful study in these fields.

During the forty years since Galton's death great advances have been made in many fields, some of which are given special attention. A full chapter provides a concise but readable review of developments in genetics, with a number of pertinent comments for students of human heredity. Another chapter discusses and attempts to evaluate various testing procedures, which Galton made to play an important role in his utopian community of "Kantsaywhere", and which in actual practice have since shown a tremendous expansion in scope and applications. With an increased diffusion of higher education, especially in a period of transition from a late expanding to a low stationary population, competition at the top will probably become ever keener and so the future may be expected to force upon us, almost against our will, more and more of these tests of fitness.

The author does not, on the whole, presume to predict much of the future, but despite the current "welter of doubts and heartsearchings", he does "surmise that Galton, were he alive today, would find grounds for hope"—and he would find some of them well stated in the final chapter on *Eugenics Today*. Means for controlling the volume of population seem to be in sight, and in much of the world there is an increasing appreciation of the seriousness of the problem that confronts us, and a growing respect for the dignity and importance of the individual. It may be hoped that our western civilization will not fail to promote the basic ideals of Galton, "a kindly man" whose "motive was to prevent, not to inflict, suffering."

There are two appendices. One is a discussion of Galton's ideas on race (which were perhaps about as objective as the current UNESCO statement on the same subject); the other lists Galton's publications from "The Telotype: a printing Electric Telegraph", published in 1849, to "Eugenics and the Jew" appearing in the Jewish Chronicle sixty-one years later.

C. H. DANFORTH
Department of Anatomy
Stanford University

Genes and Mutations

Cold Spring Harbor Symposia on Quantitative Biology, volume 16, 521 + xvi pages, quarto, 144 figures and 19 plates, published by The Biological Laboratory, Cold Spring Harbor, New York. Price $9.00 (postage extra).

A REVIEW of this symposium on "Genes and Mutations" is hardly possible in the space available, but the list of contents, giving names of authors and titles of papers, should be proof enough that the volume should be on the shelf of every geneticist, anthropologist, psychologist, physician, or sociologist who wishes to be kept up-to-date on this very interesting and important topic.

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It is a pleasure to recommend so scholarly and valuable a volume.

HERLUF H. STRANDSKOV
The University of Chicago

BIBLIOGRAPHY OF HUMAN GENETICS

PREPARED BY
V. RAE PHELPS

Department of Bacteriology, Michigan State College, East Lansing, Michigan

THIS section is a list of references to recent and current articles and books which may be of interest to students of Human Genetics. An attempt has been made and is being made to make the list complete, but to do so is a difficult task. Everyone can be of help by sending to the bibliographic editor, at the address given above, any recent reference which it seems probable may be missed because of its appearance in a journal which probably is not systematically covered. References to recently published and forthcoming books are particularly desired. If a reference is sent in, be sure that it is complete with respect to name of author, year of publication, title, name of journal (or publisher and address of publisher, if book), volume number, and first and last page numbers.

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